Update on Antiseizure Medications 2025

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REVIEW ARTICLE

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EDITOR'S NOTE
The article "Update on Antiseizure Medications 2025" by Dr Abou-Khalil was first published in the February 2016 Epilepsy issue of *Continuum: Lifelong Learning in Neurology* as "Antiepileptic Drugs," and at the request of the Editor-in-Chief was updated by Dr Abou-Khalil for the 2019 and 2022 issues and again for this issue.

ABSTRACT

OBJECTIVE: **This article is an update from the article on antiseizure medication therapy published in the three previous *Continuum* issues on epilepsy and is intended to cover the vast majority of agents currently available to neurologists in the management of patients with epilepsy. This article addresses antiseizure medications individually, focusing on key pharmacokinetic characteristics, indications, and modes of use.**

LATEST DEVELOPMENTS: **Since the most recent version of this article was published, one new antiseizure medication, ganaxolone, has been approved by the US Food and Drug Administration (FDA), and the indications of some approved medications were expanded. Older antiseizure medications are effective but have tolerability and pharmacokinetic disadvantages. Several newer antiseizure medications have undergone comparative trials demonstrating efficacy equal to and tolerability at least equal to or better than older antiseizure medications as first-line therapy for focal epilepsy. These agents include lamotrigine, oxcarbazepine, levetiracetam, topiramate, zonisamide, and lacosamide. Pregabalin was found to be less effective than lamotrigine. Lacosamide, pregabalin, and eslicarbazepine have undergone successful trials of conversion to monotherapy for focal epilepsy. Other newer antiseizure medications with a variety of mechanisms of action are suitable for adjunctive therapy.**

ESSENTIAL POINTS: **Knowledge of antiseizure medication pharmacokinetics, efficacy, and tolerability profiles facilitates the choice of appropriate antiseizure medication therapy for patients with epilepsy. Rational antiseizure medication combinations should avoid antiseizure medications with unfavorable pharmacokinetic interactions or pharmacodynamic interactions related to mechanism of action.**

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RELATIONSHIP DISCLOSURE:
The institution of Dr Abou-Khalil has received research support from Cerevel Therapeutics, Neuroelectrics, Otsuka America Pharmaceutical, Inc, SK-Pharma, UCB S. A., and Xenon Pharmaceuticals, Inc.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Abou-Khalil discusses the unlabeled/investigational use of cannabidiol and clobazam for the treatment of focal-onset seizures, gabapentin for the treatment of headache and sleep disorders, lamotrigine as a first-line treatment for epilepsy, perampanel for myoclonus, primidone for the treatment of essential tremor, valproate for the treatment of generalized myoclonic and generalized tonic-clonic seizures, and zonisamide as initial monotherapy for epilepsy.

INTRODUCTION

Antiseizure medications are the mainstay of epilepsy therapy. Until 1993, the choice of antiseizure medication was limited to seven or eight major agents. However, more than 20 new antiseizure medications have been approved and marketed since then. With such a large choice of antiseizure medications, much guidance is needed in the choice of antiseizure medications for initial therapy, later replacement monotherapy, or adjunctive therapy. Considerations in antiseizure medication choice must include the spectrum of efficacy of the antiseizure medication (TABLE 6-1), its pharmacokinetic properties (TABLE 6-2), its safety and tolerability profile, and its efficacy against comorbidities, as relevant to the patient's specific circumstances. This article addresses each antiseizure medication, focusing on indications, tolerability, and clinical use. Relevant pharmacokinetic properties are also discussed. This article focuses on antiseizure medication use in adults with suggested dosing in TABLE 6-3; however, salient features related to use in children are highlighted throughout the text. TABLE 6-4 summarizes antiseizure medication dosing in children, and TABLE 6-5[1-3] summarizes teratogenicity data for antiseizure medications. The order in which antiseizure medications are presented in this article is roughly based on the order in which they were marketed, although related antiseizure medications will be discussed together with their oldest relative.

PHENOBARBITAL

Phenobarbital has been in clinical use since 1912, although initially used as a sedative and sleep aid. Its main mechanism of action is through binding the γ-aminobutyric acid A ($GABA_A$) receptor, prolonging the opening of the associated chloride channel. It is available as an oral preparation as well as a parenteral solution. It has excellent oral bioavailability and relatively low protein binding. It is mostly metabolized in the liver, but approximately one-quarter of the dose is eliminated unchanged in the urine. It has a long half-life of approximately 80 to 100 hours. Phenobarbital is a potent hepatic P450 enzyme inducer, accelerating the metabolism of medications processed by this enzyme system and reducing their plasma concentration. This affects its use in combination therapy because it may render concomitant antiseizure medications less effective if they are metabolized by the liver.

Phenobarbital is effective against focal-onset seizures and generalized tonic-clonic seizures but is not effective against generalized absence seizures. The parenteral solution has been used effectively for status epilepticus.[4]

The suggested maintenance dose is 1 mg/kg/d to 2.5 mg/kg/d,[5] but a much lower starting dose is recommended, such as 30 mg to 60 mg at bedtime. The dose can be increased by 30 mg to 60 mg every 1 to 2 weeks as needed, depending on seizure control and tolerability. A once-daily dose at bedtime may reduce sedation and is adequate because of its long half-life. The recommended serum concentration is 15 μg/mL to 40 μg/mL.

Phenobarbital's main possible adverse effects are sedation, decreased concentration, and mood changes, particularly depression. In children, it can cause hyperactivity. Long-term use is associated with decreased bone density, Dupuytren contractures, plantar fibromatosis, and frozen shoulder. It is not recommended in pregnancy because of teratogenicity with increased risk of cardiac malformations in the exposed fetus. Evidence also exists of decreased

Spectrum of Efficacy of Select Antiseizure Medications

TABLE 6-1

Antiseizure medication	Focal seizures	Generalized tonic-clonic seizures	Generalized absence seizures	Generalized myoclonic seizures	Other[a]
Brivaracetam	Class I trials	Unknown	Unknown	Unknown	
Carbamazepine	Class I trials	Suggested, but not proven in Class I trials	Not effective	Not effective	
Cannabidiol	Class IV evidence	Unknown	Unknown	Unknown	Class I trials in Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis
Cenobamate	Class I trials	Unknown	Unknown	Unknown	
Clobazam	Suggested, but not proven in Class I trials	Suggested, but not proven in Class I trials	Suggested, but not proven in Class I trials	Suggested, but not proven in Class I trials	Class I trials in Lennox-Gastaut syndrome
Eslicarbazepine acetate	Class I trials	Unknown	Not effective	Not effective	
Ethosuximide	Not effective	Not effective	Class I trials	Not effective	
Felbamate	Class I trials	Suggested, but not proven in Class I trials	Unknown	Unknown	Class I trial in Lennox-Gastaut syndrome
Fenfluramine	Unknown	Unknown	Unknown	Unknown	Class I trial in Dravet syndrome and Lennox-Gastaut syndrome
Gabapentin	Class I trials	Not effective	Not effective	Not effective	
Ganaxolone	Unknown	Unknown	Unknown	Unknown	Class 1 trial in cyclin-dependent kinase-like 5 deficiency disorder
Lacosamide	Class I trials	Class I trials	Not effective	Not effective	
Lamotrigine	Class I trials	Class I trials	Suggested, but not proven in Class I trials	Variable	Class I trial in Lennox-Gastaut syndrome
Levetiracetam	Class I trials	Class I trials	Suggested, but not proven in Class I trials	Class I trials	
Oxcarbazepine	Class I trials	Unknown	Not effective	Not effective	
Perampanel	Class I trials	Class I trials	Unknown	Class IV evidence	
Phenobarbital	Class I trials	Suggested, but not proven in Class I trials	Not effective	Class IV evidence	

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Antiseizure medication	Focal seizures	Generalized tonic-clonic seizures	Generalized absence seizures	Generalized myoclonic seizures	Other[a]
Phenytoin	Class I trials	Suggested, but not proven in Class I trials	Not effective	Not effective	
Pregabalin	Class I trials	Not effective	Not effective	Not effective	
Rufinamide	Class I trials, but not FDA approved	Suggested, but not proven in Class I trials	Unknown	Unknown	Class I trial in Lennox-Gastaut syndrome
Stiripentol	Unknown	Unknown	Unknown	Unknown	Class I trials in Dravet syndrome
Tiagabine	Class I trials	Not effective	Not effective	Not effective	
Topiramate	Class I trials	Class I trials	Not effective in one Class I trial	Unknown	Class I trial in Lennox-Gastaut syndrome
Valproate	Class I trials	Suggested, but not proven in Class I trials	Class I trials	Suggested, but not proven in Class I trials	Suggested, but not proven in Class I trials
Vigabatrin	Class I trials	Not effective	Not effective	Not effective	Class I trial in infantile spasms
Zonisamide	Class I trials	Suggested, but not proven in Class I trials	Suggested, but not proven in Class I trials	Suggested, but not proven in Class I trials	

FDA = US Food and Drug Administration.
[a] Blank cells in this column represent no convincing or Class I data.

cognitive abilities in males exposed in utero. Phenobarbital is a controlled substance.

Place in Therapy

Because of its adverse effect on cognitive function and its enzyme induction, phenobarbital is used very infrequently as first-line therapy in high-income countries, with the exception of its use to treat neonatal seizures. However, its low cost and wide availability make it the only affordable antiseizure medication in much of the developing world. In addition, there has been some debate about adverse cognitive effects; one study in rural China reported no major negative cognitive effects, and some cognitive gains, likely related to improved seizure control.[6]

PRIMIDONE

Primidone is converted in the liver to phenobarbital and phenylethylmalonamide, which is also an active metabolite. It is available only as an oral preparation. When used in monotherapy, about 25% of oral primidone is converted to phenobarbital. The half-life of primidone is 10 to 15 hours in

Select Pharmacokinetic Parameters of Antiseizure Medications

TABLE 6-2

Antiseizure medication	Key mechanisms of action	Oral bioavailability	Protein binding[a]	Metabolism/ elimination	Half-life (in adults, in absence of inducers or inhibitors)	Potential for pharmacokinetic interactions
Brivaracetam	Binding SV2A	Good	Low	Extensive hepatic	Approximately 7-8 hours	Moderate
Carbamazepine	Blocking sodium channels	Good	Intermediate	Extensive hepatic	12-17 hours (after autoinduction is complete)	High
Cannabidiol	Enhancing GABA, modulation of intracellular calcium	Low	High	Extensive hepatic	56-61 hours	High
Cenobamate	Blocking sodium channels, enhancing GABA	Good	Intermediate	Extensive hepatic	50-60 hours	High
Clobazam	Enhancing GABA	Good	High	Extensive hepatic	10-30 hours, 36-46 hours for active *N*-desmethylclobazam metabolite	High
Eslicarbazepine acetate	Blocking sodium channels	Good	Low	Approximately 40% hepatic, 60% renal unchanged	13-20 hours	Moderate
Ethosuximide	Blocking T-type calcium channels	Good	Low	Extensive hepatic	30-60 hours	Moderate
Felbamate	NMDA antagonism, blocking sodium channels, enhancing GABA	Good	Low	Approximately 50% hepatic, 40-50% unchanged in urine	20-23 hours	High
Fenfluramine	Enhancing serotonin	Low	Intermediate	>75% hepatic, <25% unchanged or active metabolite in urine	Approximately 20 hours	High
Gabapentin	Binding α2δ calcium channel subunit	Low	Low	None	5-7 hours	None or minimal

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Antiseizure medication	Key mechanisms of action	Oral bioavailability	Protein binding[a]	Metabolism/ elimination	Half-life (in adults, in absence of inducers or inhibitors)	Potential for pharmacokinetic interactions
Ganaxolone	Enhancing GABA	Low	High	Extensive hepatic	Approximately 34 hours	Moderate
Lacosamide	Blocking sodium channels	Good	Low	Approximately 60% hepatic, 40% unchanged in urine	Approximately 13 hours	None or minimal
Lamotrigine	Blocking sodium channels	Good	Intermediate	Extensive hepatic	Approximately 24 hours	Moderate
Levetiracetam	Binding SV2A	Good	Low	Approximately 30% nonhepatic, 66% unchanged renal	6-8 hours	None or minimal
Oxcarbazepine	Blocking sodium channels	Good	Low	Extensive hepatic	8-10 hours (for active metabolite)	Moderate
Perampanel	AMPA antagonism	Good	High	Extensive hepatic	Approximately 105 hours	Moderate
Phenobarbital	Enhancing GABA	Good	Low	>70% metabolized in liver, 20-25% eliminated renally unchanged	80-100 hours	High
Phenytoin	Blocking sodium channels	Variable	High	Extensive hepatic, nonlinear	Average 22 hours (longer with toxicity)	High
Pregabalin	Binding α2δ calcium channel subunit	Good	Low	None	Approximately 6 hours	None or minimal
Primidone	Enhancing GABA	Good	Low	25% converted to phenobarbital, 40% excreted unchanged in urine	10-15 hours	High
Rufinamide	Blocking sodium channels	Good	Intermediate	Extensive hepatic	6-10 hours	Moderate

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Antiseizure medication	Key mechanisms of action	Oral bioavailability	Protein binding[a]	Metabolism/ elimination	Half-life (in adults, in absence of inducers or inhibitors)	Potential for pharmacokinetic interactions
Stiripentol	Enhancing GABA	Good	High	Extensive hepatic	4.5-13 hours	High
Tiagabine	Enhancing GABA	Good	High	Extensive hepatic	7-9 hours	High
Topiramate	Blocking sodium channels, AMPA/ glutamate antagonism, enhancing GABA	Good	Low	Approximately 30% hepatic, 70% unchanged in urine	Approximately 21 hours	None or minimal
Valproate	Blocking sodium channels, enhancing GABA, blocking T-type calcium channels	Good	High	Extensive hepatic	13-16 hours	High
Vigabatrin	Enhancing GABA	Good	Low	None	Approximately 10.5 hours	None or minimal
Zonisamide	Blocking sodium channels, blocking T-type calcium channels	Good	Low	Approximately 65%	Approximately 60 hours	Moderate

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA = γ-aminobutyric acid; NMDA = *N*-methyl-D-aspartate.
[a] Low: <50%; intermediate: 50% to 85%; high: >85%.

monotherapy and 6.5 to 8.3 hours with enzyme inducers. Primidone is a potent enzyme inducer.

Primidone is effective against focal-onset seizures and generalized tonic-clonic seizures. Anecdotal evidence also exists of efficacy against myoclonic seizures in juvenile myoclonic epilepsy. Primidone is also effective in controlling essential tremor.[7]

In addition to sedation and other adverse effects of phenobarbital, primidone use may be associated with an acute toxic reaction unrelated to phenobarbital, with potentially debilitating drowsiness, dizziness, ataxia, nausea, and vomiting.

Place in Therapy

Primidone was the least-tolerated agent in the large cooperative US Department of Veterans Affairs trial comparing the efficacy and tolerability of

TABLE 6-3 **Suggested Adult Antiseizure Medication Dosing**

Antiseizure medication	Starting total daily dose	Titration	Initial target total daily dose; usual maximal dose (for some antiseizure medications)[a]
Brivaracetam	50-100 mg	50 mg as needed	100 mg; maximum 200 mg
Carbamazepine	200 mg	200 mg every 3 days	400-800 mg
Cannabidiol	5 mg/kg	Increase by 5 mg/kg every week as needed	10 mg/kg; maximum 20 mg/kg
Cenobamate	12.5 mg	Increase to 25 mg after 2 weeks, 50 mg 2 weeks later, then by 50 mg/2 wk	100-200 mg; maximum 400 mg
Clobazam	10 mg	10 mg/2 wk as needed	20-40 mg
Eslicarbazepine acetate	400 mg	400 mg/wk as needed	800-1200 mg; maximum 1600 mg
Ethosuximide	500 mg	250 mg/wk as needed	750 mg; maximum 1500 mg
Felbamate	1200 mg	600-1200 mg/wk	3600 mg
Gabapentin	300-400 mg	300-400 mg/d	1200 mg; maximum 4800 mg
Ganaxolone	450 mg	450 mg/wk	1800 mg
Lacosamide	100 mg	100 mg/wk as needed	200 mg; maximum 600 mg
Lamotrigine	Monotherapy for weeks 1 and 2: 25 mg	Monotherapy for weeks 3 and 4: 50 mg; then increase by 50 mg every 1-2 weeks	200-300 mg
Levetiracetam	500 mg	500 mg/wk as needed	1000 mg; maximum 4000 mg
Oxcarbazepine	300-600 mg	300 mg/wk as needed	600-1200 mg; maximum 2400 mg
Perampanel	2 mg	2 mg/3 wk	4 mg; maximum 8 mg
Phenobarbital	30-60 mg	30-60 mg every 1-2 wk as needed	120-180 mg
Phenytoin	200-400 mg	No titration needed, dose adjustment with 30- to 60-mg increments as needed for seizure control	200-400 mg
Pregabalin	75-150 mg	75-150 mg/wk as needed	300 mg; maximum 600 mg
Primidone	50-125 mg	50-125 mg every 3-7 days	750-1000 mg
Rufinamide	400 mg	400 mg every 2 days	3200 mg
Tiagabine	4 mg	4 mg/wk	24 mg; maximum 56 mg
Topiramate	25 mg	25 mg/wk	100 mg; maximum 400 mg
Valproate	500 mg	250-500 mg/wk as needed	1000-2000 mg
Vigabatrin	1000 mg	500 mg/wk as needed	3000 mg; maximum 6000 mg
Zonisamide	100 mg	100 mg/1-2 wk as needed	200 mg; maximum 600 mg

[a] The schedule depends on the formulation used and the half-life of the antiseizure medication.

Suggested Pediatric Antiseizure Medication Dosing[a]

TABLE 6-4

Antiseizure medication	Starting total daily dose	Titration	Target total daily dose; usual maximal effective dose
Brivaracetam[b]	1-2 mg/kg/d	Dose adjustment based on response	1-5 mg/kg/d (pediatric patients weighing >50 kg [110 lb]: initial dose of 50-100 mg/d with maximum dose of 200 mg/d)
Carbamazepine	10-20 mg/kg/d	Increase weekly using 100-mg increments	20 mg/kg/d; usually <35 mg/kg/d
Cannabidiol	5 mg/kg/d	Increase by 5 mg/kg/d every week as needed	20 mg/kg/d
Clobazam	0.1 mg/kg/d	Increase by 0.1 mg/kg/d every week as needed	0.5-1.0 mg/kg/d
Eslicarbazepine acetate	10-20 mg/kg/d (200-400 mg/d depending on weight)	200-400 mg/wk as needed	20-60 mg/kg/d (400-1200 mg/d depending on weight)
Ethosuximide	10-15 mg/kg/d	5 mg/kg/d every week as needed	20-30 mg/kg/d; up to 40 mg/kg/d
Felbamate	15 mg/kg/d	15 mg/kg/d every week	45 mg/kg/d
Fenfluramine	0.2 mg/kg/d	Increase weekly as needed	0.7 mg/kg/d; maximum of 26 mg/d 0.4 mg/kg/d in presence of stiripentol and clobazam; maximum 17 mg/d
Gabapentin	10-15 mg/kg/d	10 mg/kg/d every day	40 mg/kg/d; up to 50 mg/kg/d
Ganaxolone	18 mg/kg/d	5 mg/kg/d every week	63 mg/kg/d
Lacosamide[b]	2 mg/kg/d	2 mg/kg/d every week	4-8 mg/kg/d 6-12 mg/kg/d for patients weighing <30 kg (66 lb)
Lamotrigine	Monotherapy for weeks 1 and 2: 0.3 mg/kg/d With valproate for weeks 1 and 2: 0.15 mg/kg/d With enzyme-inducer for weeks 1 and 2: 0.6 mg/kg/d	Monotherapy for weeks 3 and 4: 0.6 mg/kg/d; week 5 and on: increase by 0.6 mg/kg/d every 1-2 weeks With valproate for weeks 3 and 4: 0.3 mg/kg/d; week 5 and on: increase by 0.3 mg/kg/d every 1-2 weeks With enzyme-inducer for weeks 3 and 4: 1.2 mg/kg/d; week 5 and on: increase by 1.2 mg/kg/d every 1-2 weeks	Maintenance dose for monotherapy: 4.5-7.5 mg/kg/d With valproate: 1-5 mg/kg/d With enzyme-inducers: 5-15 mg/kg/d
Levetiracetam	20 mg/kg/d (infants 1 month to <6 months of age: 14 mg/kg/d)	10 mg/kg/d every 1-2 weeks	Children 4 years to <16 years: 60 mg/kg/d; children 6 months to <4 years: 50 mg/kg/d; infants 1 month to <6 months: 42 mg/kg/d
Oxcarbazepine	8-10 mg/kg/d	5-10 mg/kg/d every 3-7 days as needed	30-50 mg/kg/d; usually <60 mg/kg/d

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Antiseizure medication	Starting total daily dose	Titration	Target total daily dose; usual maximal effective dose
Perampanel	2 mg/d	Increase by 2 mg as needed, no more frequently than weekly	8-12 mg/d
Phenobarbital	1-3 mg/kg/d	1 mg/kg/d every 1-2 weeks	3 mg/kg/d; up to 8 mg/kg/d
Phenytoin	5-7 mg/kg/d	No titration needed	6-8 mg/kg/d; up to 10 mg/kg/d (may be guided by serum concentration)
Pregabalin	2.5 mg/kg/d if patient weighs ≥30 kg (66 lb) 3.5 mg/kg/d if patient weighs <30 kg (66 lb)	Increase by 2.5 mg/kg/d weekly as needed	10 mg/kg if patient weighs ≥30 kg (66 lb) 14 mg/kg if patient weighs <30 kg (66 lb)
Rufinamide	10 mg/kg/d With valproate, the starting dose should be approximately 5 mg/kg/d	Increase by 10 mg/kg/d every other day With valproate, titration rate should be approximately 5 mg/kg/d every other day	45 mg/kg/d With valproate, target dose should be 20-30 mg/kg/d
Stiripentol	50 mg/kg/d		3000 mg/d
Topiramate	1-3 mg/kg/d	1-3 mg/kg/d every 1-2 weeks	5-9 mg/kg/d
Valproate	15 mg/kg/d	5-10 mg/kg/d every week	30 mg/kg/d; up to 60 mg/kg/d with enzyme-inducing antiseizure medications
Vigabatrin	20 mg/kg/d Infantile spasms: 50 mg/kg/d	20 mg/kg/d every week as needed Infantile spasms: increase to 100 mg/kg/d after 5 days	40-60 mg/kg/d Infantile spasms: 100 mg/kg/d; maximum 150 mg/kg/d
Zonisamide[c]	1 mg/kg/d	2 mg/kg/d every 2 weeks as needed	Usual dose of 4-8 mg/kg/d; with maximum dose of 12 mg/kg/d

[a] Generally applicable to children younger than 12 years. The dosing is provided for antiseizure medications that have at least been tested in children.
[b] Applicable to children weighing 11-50 kg (24-110 lb).
[c] Not US Food and Drug Administration (FDA)-approved for children.

carbamazepine, phenobarbital, phenytoin, and primidone in adult patients with previously untreated or undertreated focal epilepsy.[8] As a result, it is infrequently used. In view of the acute toxic adverse effects, primidone should be started at a low dose, for example, 50 mg to 125 mg at bedtime, then increased gradually by 50 mg to 125 mg every 3 to 7 days to 250 mg 3 times a day.

PHENYTOIN

Phenytoin has been in clinical use since 1938 when its efficacy in the maximum electroshock animal model was discovered. Phenytoin binds to the active state of the sodium channel to prolong its fast inactivated state, thus reducing high-frequency firing as might occur during a seizure, while allowing normal action potentials to occur. It is available as an oral preparation and a parenteral solution,

Antiseizure Medication Teratogenicity[a]

TABLE 6-5

Antiseizure medication	Number of women with monotherapy exposure (if >100)	Major malformation rate[b]
Brivaracetam	Insufficient exposure	Unknown
Carbamazepine	>4800	Intermediate
Cannabidiol	Insufficient exposure	Unknown
Cenobamate	Insufficient exposure	Unknown
Clobazam	Insufficient exposure	Unknown
Clonazepam	>100	Low
Eslicarbazepine acetate	Insufficient exposure	Unknown
Ethosuximide	Insufficient exposure	Unknown
Felbamate	Insufficient exposure	Unknown
Fenfluramine	Insufficient exposure	Unknown
Gabapentin	>200	Low
Ganaxolone	Insufficient exposure	Unknown
Lacosamide	Insufficient exposure	Unknown
Lamotrigine	>7000	Low
Levetiracetam	>2100	Low
Oxcarbazepine	>600	Low
Perampanel	Insufficient exposure	Unknown
Phenobarbital[c]	>500	High
Phenytoin	>600	Intermediate
Pregabalin	Insufficient exposure	Unknown
Primidone	Insufficient exposure	Unknown
Rufinamide	Insufficient exposure	Unknown
Stiripentol	Insufficient exposure	Unknown
Tiagabine	Insufficient exposure	Unknown
Topiramate	>700	Intermediate
Valproate[d]	>2900	Very high
Vigabatrin	Insufficient exposure	Unknown
Zonisamide	>200	Low

[a] Data are extracted from North American, European, and UK registries.[1-3] A weighted average was used. Data reported only for antiseizure medications with >100 monotherapy exposures.
[b] Low: ≤3%; intermediate: 3.1% to 6%; high: 6.1% to 8%; very high: >8%.
[c] An additional negative effect is decreased IQ in male offspring.
[d] Additional negative effects are decreased verbal IQ and autism.

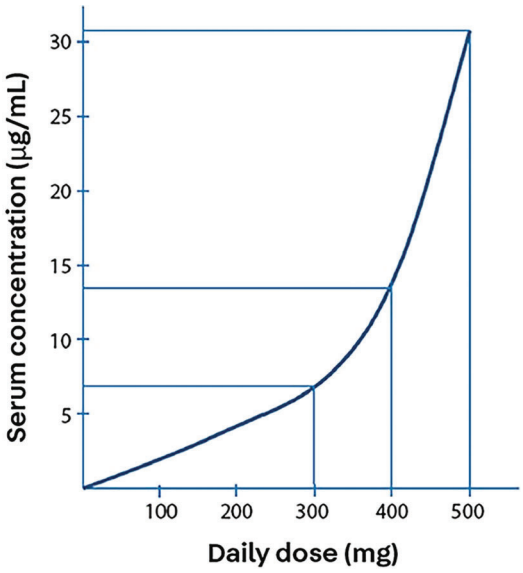

FIGURE 6-1
Example of the nonlinear kinetics of phenytoin. An increase in the daily dose beyond 300 mg is associated with a disproportionate increase in serum concentration. At a dose of 400 mg/d, the serum concentration is about 13 μg/mL. If seizures are still not controlled at this dose, an increment of 100 mg pushes the serum concentration beyond 30 μg/mL, with a high risk of clinical toxicity. An increment of 30 mg would be more appropriate.

and a phenytoin prodrug, fosphenytoin, is available for IV and IM administration.

Phenytoin bioavailability is reduced with coadministration of calcium, antacids, and nasogastric feedings. It is highly protein bound at approximately 90%. It is metabolized in the liver, mostly by cytochrome P450 (CYP) 2C9 and, to a lesser extent, CYP2C19. Phenytoin's metabolism is saturable, resulting in nonlinear kinetics. As the serum concentration increases, it reaches a point within the recommended therapeutic range after which the half-life starts increasing. Beyond that point, the phenytoin plasma level increases disproportionately with an increase in the dose (FIGURE 6-1).

Phenytoin is a potent enzyme inducer that reduces the efficacy of drugs metabolized by the P450 enzyme system. Phenytoin is also affected by several agents that reduce its metabolism and cause it to accumulate. These include amiodarone, fluoxetine, fluvoxamine, isoniazid, and azole antifungal agents. The phenytoin protein-free fraction may increase with hepatic and renal failure, in low-protein states, during pregnancy, in people older than 50 years, and in the presence of highly protein-bound drugs, such as valproate, that compete for protein binding. This is clinically relevant when decisions are made based on total phenytoin serum concentration.

Phenytoin is effective against focal-onset seizures and generalized tonic-clonic seizures. Phenytoin is not effective against generalized myoclonic or generalized absence seizures and may even exacerbate these seizures; hence, it is not a drug of choice in idiopathic generalized epilepsy.

The usual phenytoin initiation dose is 200 mg/d to 400 mg/d, initially given as a bedtime dose. Titration is primarily based on clinical response but also takes into consideration the serum concentration. The recommended "therapeutic" serum concentration is 10 μg/mL to 20 μg/mL; the protein-free recommended "therapeutic" serum concentration is 1 μg/mL to 2 μg/mL. Protein-free phenytoin levels should be checked in clinical situations in which the protein-free fraction is expected to be increased. In view of nonlinear kinetics, small increments (eg, 30 mg to 60 mg) should be used when the phenytoin level is in the "therapeutic range," but the clinical situation warrants optimization of therapy. Extended-release capsules are preferred. Dosing 2 times a day may be needed when seizures are drug resistant. Phenytoin can be loaded orally at 18 mg/kg divided into 3 doses given 2 to 3 hours apart (or even as a single dose if needed).

The IV preparation of phenytoin may be associated with local reactions, including burning pain, phlebitis, cellulitis, and, rarely, the purple glove syndrome. IM administration is contraindicated because of erratic absorption and sterile abscess formation. The phenytoin water-soluble prodrug fosphenytoin is preferred for parenteral use. It has a lower incidence of local reactions with IV administration. It is also well absorbed after IM administration, which can be considered in the absence of IV access. When administered intravenously in an awake individual, it may be associated with paresthesia and pruritus, most often in the groin region. IV administration of either phenytoin or fosphenytoin can be associated with hypotension and arrhythmias, so ECG and blood pressure monitoring are recommended, and the rate of IV administration should not exceed 50 mg/min for phenytoin and 150 mg/min for fosphenytoin.

Phenytoin is less sedating than phenobarbital but nevertheless may have cognitive adverse effects in some individuals, even within the therapeutic range. Adverse effects that occur with high concentrations include ataxia, incoordination, dysarthria, nystagmus, and diplopia. A paradoxical increase in seizures has been documented with concentrations exceeding 30 μg/mL. Idiosyncratic reactions may include allergic rash (almost 6% in a study based on clinical practice)[9] and, rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, or hypersensitivity syndrome with fever, rash, lymphadenopathy, eosinophilia, and liver and renal impairment. Adverse effects associated with long-term use include gingival hyperplasia, acne, hirsutism, cerebellar atrophy, decreased bone density, anemia, and peripheral neuropathy.

Place in Therapy

Phenytoin was the most frequently used antiseizure medication for many years, but its use has declined considerably since the appearance of newer antiseizure medications with improved tolerability and pharmacokinetic profiles. Other factors in its declining use are its narrow therapeutic window and the challenge in maintaining the recommended therapeutic concentration range without producing toxicity or underdosing, because of nonlinear kinetics as well as variable absorption.

CARBAMAZEPINE

Carbamazepine's mechanism of action is similar to that of phenytoin. It blocks the sodium channel in a voltage-dependent and use-dependent fashion, reducing high-frequency neuronal firing.

Carbamazepine was only available as an oral preparation until a parenteral preparation was approved in 2016 as temporary replacement therapy when oral administration is not feasible. Carbamazepine has good oral bioavailability. Its protein binding of about 75% is not of clinical importance. It is metabolized in the liver, mainly by CYP3A4; the most important metabolite is carbamazepine-10, 11-epoxide. It is an active metabolite also responsible for some adverse effects. Carbamazepine is a potent enzyme inducer, reducing the levels of drugs as well as endogenous substances metabolized by the CYP enzyme system. Carbamazepine also induces its own metabolism, a process known as *autoinduction*, which results in increased clearance over 2 to 4 weeks, with shortened half-life and lower serum concentration. Carbamazepine may accumulate when coadministered with inhibitors of CYP3A4, such as

KEY POINTS

- In addition to sedation and other adverse effects of phenobarbital, primidone use may be associated with an acute toxic reaction unrelated to phenobarbital, with potentially debilitating drowsiness, dizziness, ataxia, nausea, and vomiting.
- Phenobarbital, primidone, phenytoin, and carbamazepine are potent inducers of liver enzymes, reducing the efficacy of drugs metabolized by the cytochrome P450 enzyme system.
- Long-term phenobarbital use is associated with decreased bone density, Dupuytren contractures, plantar fibromatosis, and frozen shoulder.
- Phenytoin has saturable nonlinear kinetics. Beyond a certain serum concentration, usually within the accepted therapeutic range, phenytoin concentration increases disproportionately with an increase in the dose. Small increments are necessary when increasing the dose at a serum concentration in the therapeutic range.
- The traditional sodium channel blockers phenytoin, carbamazepine, and oxcarbazepine may exacerbate generalized absence and myoclonic seizures and should be avoided in idiopathic generalized epilepsy. Other antiseizure medications that have similar potential are gabapentin, pregabalin, tiagabine, and vigabatrin.

erythromycin and other macrolide antibiotics (except azithromycin), fluoxetine, propoxyphene, and grapefruit juice. Carbamazepine epoxide levels increase with concomitant use of some inhibitors, such as valproate and felbamate, and with brivaracetam.

Carbamazepine is effective against focal-onset seizures and generalized tonic-clonic seizures. However, it may exacerbate absence, myoclonic, and atonic seizures. Hence, it is not a good choice in idiopathic generalized epilepsy. It has US Food and Drug Administration (FDA) indications for trigeminal neuralgia and for acute mania and bipolar disorder. The starting dose is 100 mg 2 times a day or 200 mg at bedtime when the extended-release preparation is used. The dose can be increased by 200 mg every 3 days to a target total daily dosage of 400 mg to 800 mg in 2 divided doses, and the dose can be increased further, if needed, for persistent seizures. When immediate-release formulations of carbamazepine are used, administration in 3 divided doses is recommended, although patients may have difficulty adhering to this more complex dosing schedule. The extended-release preparation, indicated for dosing 2 times a day, provides steadier levels with evidence for improved tolerability as well as efficacy.[10,11] The recommended therapeutic range of carbamazepine concentration is 4 μg/mL to 12 μg/mL.

Adverse effects noted with carbamazepine may include nausea, dizziness, sedation, and tiredness. Cognitive impairment has been reported on neuropsychological testing.[12] With elevated levels, there may be blurred vision, diplopia, nystagmus, unsteadiness, incoordination, and tremor. Hyponatremia may occur. Weight gain and decreased bone density are reported with long-term use. Mild leukopenia seen in 10% to 20% of patients is usually benign, although it may be persistent; the more serious aplastic anemia is rare (estimated at 1 in 200,000). It is advisable to check a complete blood cell count and liver enzymes before initiating therapy, after 2 to 3 months of treatment, then every 6 to 12 months as needed depending on the clinical setting. Idiosyncratic adverse experiences may include rash, which may be less common than with phenytoin. Stevens-Johnson syndrome and toxic epidermal necrolysis are rare but more likely with the HLA-B1502 allele in individuals of Asian descent, for whom genetic testing of HLA-B polymorphisms is indicated before initiation. Other rare idiosyncratic adverse effects may include a lupuslike syndrome, hepatotoxicity, and hypersensitivity syndrome with fever, rash, and organ involvement. Carbamazepine use in polytherapy has been associated with increased risk of spina bifida in infants exposed during gestation. Abrupt withdrawal may be associated with severe rebound seizures.[13,14]

Place in Therapy

Carbamazepine had the best balance of efficacy and tolerability in the large cooperative US Department of Veterans Affairs study that also included phenytoin, phenobarbital, and primidone.[8] As a result, it became the standard treatment for focal-onset seizures. No drug has been demonstrated to be more effective than carbamazepine, but its use has declined with the marketing of new antiseizure medications that have pharmacokinetic advantages. Lamotrigine, oxcarbazepine, and gabapentin have better tolerability than immediate-release carbamazepine.[15-21] However, comparative trials using extended-release carbamazepine have failed to show superior tolerability of lamotrigine, levetiracetam, zonisamide, or lacosamide.[22-26] Nevertheless, enzyme induction

and pharmacokinetic interactions have been issues favoring newer antiseizure medications, but economic considerations favor the less-expensive carbamazepine.

OXCARBAZEPINE

Oxcarbazepine is a structural analogue of carbamazepine, but the minor structural differences result in major differences in metabolism and induction of metabolic pathways. Like carbamazepine and phenytoin, oxcarbazepine binds to the sodium channel, inhibiting high-frequency repetitive neuronal firing. Oxcarbazepine is only available as an oral preparation.

Oxcarbazepine has excellent oral bioavailability. It is very rapidly converted to the monohydroxy derivative, which has two enantiomers, the active S-licarbazepine, responsible for most of oxcarbazepine's antiseizure activity (80%), and R-licarbazepine (less active but contributes to adverse effects). Its protein binding is not clinically important. The half-life of oxcarbazepine is only 1 to 3.7 hours, and that of the monohydroxy derivatives is 8 to 10 hours. Oxcarbazepine is a weak inducer of CYP3A4, which is responsible for estrogen metabolism, and reduces the efficacy of the oral contraceptive pill at high doses, usually greater than 900 mg/d. It is a weak inhibitor of CYP2C19, thus raising the phenytoin level when used at high doses. It does not induce its own metabolism. Unlike carbamazepine, it is not affected by CYP3A4 inhibitors, such as erythromycin, fluoxetine, propoxyphene, and grapefruit juice.

Oxcarbazepine is effective against focal-onset seizures. It may exacerbate absence and myoclonic seizures and should be avoided in patients with generalized epilepsy. It can be started at a dose of 300 mg 2 times a day, but in the absence of urgency, it is better to start at 150 mg 2 times a day. The dose can be titrated by 300 mg/wk as needed. The highest dose used in clinical trials was 1200 mg 2 times a day. An extended-release preparation is available, allowing for once-daily dosing. The recommended therapeutic range for the monohydroxy derivative is 15 μg/mL to 35 μg/mL. Conversion from carbamazepine can be made overnight by using 300 mg of oxcarbazepine for every 200 mg of carbamazepine when the carbamazepine dose is 800 mg or less. A slower conversion and lower ratio are advisable with higher carbamazepine doses. Conversion from carbamazepine may be accompanied by reduction in sodium concentration and increased levels of concomitant medications metabolized by the CYP enzyme system.

Oxcarbazepine may cause drowsiness, headache, and fatigue. Higher doses can cause dizziness, blurred vision, diplopia, nausea, vomiting, and ataxia. Rash may occur in 2% to 4% of individuals; oxcarbazepine has 25% cross-reactivity with carbamazepine. Oxcarbazepine is more likely to cause hyponatremia than carbamazepine[27,28]; symptomatic hyponatremia is more likely in older individuals and those taking a diuretic. Abrupt withdrawal may be associated with severe rebound seizures.[29]

Place in Therapy

Oxcarbazepine is approved as a first-line monotherapy for focal-onset seizures. Multiple comparative monotherapy trials for new-onset focal epilepsy have demonstrated that oxcarbazepine is equal in efficacy to phenytoin and immediate-release carbamazepine but with possibly superior tolerability.[30,31] Combining oxcarbazepine with other classic sodium channel blockers, such as

KEY POINTS

- Unlike phenytoin, the phenytoin prodrug fosphenytoin may be administered intramuscularly, with reliable absorption, in the absence of IV access.
- Carbamazepine induces its own metabolism, so it has to be titrated gradually to the target dose.
- The HLA-B1502 allele is predictive of a carbamazepine-induced severe rash in individuals of Asian descent.

carbamazepine, lamotrigine, and phenytoin, may limit tolerability because of dizziness, diplopia, and ataxia.

ESLICARBAZEPINE ACETATE

Eslicarbazepine acetate was approved for marketing in the United States in 2014, but it is listed here because it represents a third-generation relative of carbamazepine and oxcarbazepine. It is a prodrug rapidly converted to the active metabolite S-licarbazepine, also known as *eslicarbazepine*, the active enantiomer of the monohydroxy derivative of oxcarbazepine. Eslicarbazepine acts by blocking sodium channels and stabilizing the inactive state of the voltage-gated sodium channel (Na_V). Two studies suggested that, unlike carbamazepine, it may enhance slow inactivation of Na_Vs.[32,33] It is available only as an oral preparation.

Eslicarbazepine is metabolized to inactive compounds, but more than 50% is excreted in the urine as unchanged eslicarbazepine. The half-life of eslicarbazepine is 13 to 20 hours in plasma and 20 to 24 hours in CSF, justifying once-daily dosing. Unlike oxcarbazepine, eslicarbazepine acetate is not followed by a CSF spike, which is suspected to be responsible for acute adverse effects.[34]

Eslicarbazepine is a weak inducer of CYP3A4, potentially decreasing plasma concentrations of estrogen and other molecules metabolized by this enzyme, and a weak inhibitor of CYP2C19, potentially increasing the plasma concentration of phenytoin and other drugs metabolized by this enzyme.

Eslicarbazepine acetate is effective against focal-onset seizures. The recommended starting dose is 400 mg once daily, to be increased to 800 mg once daily after 1 week. If needed, the dose can be increased again to 1200 mg/d after 1 week. In a successful conversion to monotherapy study, a dose of 1600 mg/d was used.[35] However, in an initial monotherapy study that allowed dosing levels of 800 mg/d, 1200 mg/d, and 1600 mg/d, two-thirds of patients did not require titration beyond 800 mg/d throughout the 6 months of treatment,[26] and the vast majority of patients maintained this dose during long-term follow-up.[36]

Eslicarbazepine acetate has adverse effects similar to oxcarbazepine, although less frequent. The most common possible dose-related adverse effects are dizziness, somnolence, headache, diplopia, nausea, vomiting, fatigue, and ataxia. Hyponatremia was less commonly reported than in oxcarbazepine trials. Sodium levels of 125 mEq/L or lower were reported in up to 1.5% of individuals taking 1200 mg/d. Rash occurs in up to 3% of individuals at 1200 mg/d. It had less pronounced neuropsychological adverse effects than carbamazepine.[37] A small prospective study suggested no adverse effect on bone density.[38]

Place in Therapy

Eslicarbazepine acetate was first approved by the FDA as adjunctive treatment for focal-onset seizures. It is best to avoid combining it with a classic sodium channel drug, although the combination with lamotrigine is less problematic than with carbamazepine.[39] A monotherapy indication followed after successful completion of a conversion to monotherapy trial.[35] Like oxcarbazepine, it should be avoided in idiopathic generalized epilepsy. Eslicarbazepine acetate could be considered a first-line monotherapy for focal-onset seizures, with tolerability advantages over immediate-release oxcarbazepine. However, financial considerations may be an obstacle.

VALPROIC ACID AND DIVALPROEX SODIUM (VALPROATE)

Valproic acid and its derivatives have multiple mechanisms of action, including GABA potentiation, blocking of T-type calcium channels (predictive of efficacy against absence seizures), and blocking of sodium channels. It is available as oral preparations (mainly in the form of divalproex sodium, a complex of valproic acid and sodium valproate) and parenteral valproate sodium preparation. Oral bioavailability is almost complete, although slightly less for the extended-release preparation. It is highly protein bound at about 90%. The free fraction increases with increasing total concentration and with coadministration of phenytoin, with which it competes for protein binding.

Valproate is extensively metabolized by conjugation and oxidation. The half-life in adults is 13 to 16 hours but shorter at about 9 hours with enzyme-inducing drugs. It is a potent enzyme inhibitor, reducing the clearance of phenobarbital, lamotrigine, rufinamide, and carbamazepine epoxide.

Valproate has a broad spectrum of efficacy against all focal and generalized seizures, including generalized absence and myoclonic seizures. The divalproex sodium formulation also has FDA indications for migraine prophylaxis and bipolar disorder. It should be started at a low dose to improve tolerability. The extended-release divalproex sodium preparation, which can be administered once daily, is preferred. The recommended starting dose is 500 mg at bedtime for the extended-release divalproex sodium preparation or 250 mg 2 times a day for the delayed-release and immediate-release preparations. The dose can be increased gradually as needed to achieve seizure control, up to 1000 mg/d to 2000 mg/d. It should be avoided in female patients of childbearing potential because of teratogenic risk. The recommended therapeutic serum concentration range is 50 μg/mL to 100 μg/mL. A protein-free concentration should be checked at high levels and in other circumstances in which the protein-free fraction is expected to rise.

The adverse effects of valproate may include gastric irritation with nausea, vomiting, and anorexia. Other possible adverse effects include diarrhea, fatigue, drowsiness, tremor, weight gain, hair loss, peripheral edema, and confusion. Tolerability is generally improved with the extended-release formulation.[40,41] Dose-related thrombocytopenia may occur. Endocrine effects are most recognized in women and include polycystic ovary syndrome, hyperandrogenism, hyperinsulinemia, and insulin resistance.[42,43] Reversible parkinsonism, gait disorder, dementia, and brain atrophy have been described with chronic use in seniors. Encephalopathy and hyperammonemia may occur in polytherapy.

Idiosyncratic hepatotoxicity and pancreatitis are potentially life-threatening but rare. Risk factors are polytherapy and young age. Valproate is associated with a dose-related teratogenicity rate higher than any other marketed antiseizure medication, with risk of major malformations higher than 20% at doses greater than 1500 mg/d.[44] In utero exposure is also associated with dose-dependent reduced verbal IQ, other cognitive dysfunction, and autism.[45-47]

Place in Therapy

Valproate remains the most effective antiseizure medication for idiopathic generalized epilepsy with generalized tonic-clonic seizures and should remain a drug of first choice for male patients with generalized epilepsy.[48,49] Although equally effective as ethosuximide for generalized absence seizures in children, it has more cognitive adverse effects.[50,51] A large cooperative US Department of

KEY POINTS

- **Oxcarbazepine is more likely to cause hyponatremia than carbamazepine. Older individuals taking a diuretic are at particularly high risk.**
- **Eslicarbazepine has a long half-life in CSF, justifying once-daily oral dosing.**

Veterans Affairs study found it less well tolerated and less effective than carbamazepine for focal impaired awareness seizures, although equally effective for focal to bilateral tonic-clonic seizures.[52]

ETHOSUXIMIDE

Ethosuximide blocks T-type calcium currents, which predicts efficacy against absence seizures. It has excellent oral bioavailability (greater than 90%). Protein binding is very low. Ethosuximide is extensively metabolized in the liver. It has a long half-life of 30 to 60 hours.

Ethosuximide is a narrow-spectrum antiseizure medication, indicated only for generalized absence seizures. The starting dose is 250 mg/d for patients between 3 and 6 years of age and 250 mg 2 times a day for those older than 6 years. The dose can be increased by 250 mg every week as needed for persistent seizures, not to exceed 500 mg 3 times a day. The recommended therapeutic range is 40 μg/mL to 100 μg/mL.

Adverse effects may include nausea, abdominal discomfort, anorexia, vomiting, diarrhea, drowsiness, insomnia, nervousness, dizziness, fatigue, ataxia, and behavior changes. Most adverse effects are dose related and are helped by administration of divided doses with meals. Headaches, psychosis, depression, and hallucinations are not clearly dose related. Idiosyncratic adverse experiences include rash, Stevens-Johnson syndrome, systemic lupus erythematosus, rare aplastic anemia, thrombocytopenia, agranulocytosis, and rare autoimmune thyroiditis.

Place in Therapy

Ethosuximide is the antiseizure medication of choice for absence epilepsy with generalized absence seizures as the only seizure type, a status supported by the large multicenter double-blind randomized controlled trial comparing ethosuximide, valproic acid, and lamotrigine.[51,53]

BENZODIAZEPINES

Benzodiazepines act mainly on the $GABA_A$ receptor, increasing the frequency of GABA-mediated chloride channel openings. Clobazam is the only 1,5-benzodiazepine, referring to the position of nitrogen atoms in the heterocyclic ring; other benzodiazepines are 1,4-benzodiazepines. Only clonazepam and clobazam, used for chronic epilepsy management, are discussed here. In the United States, they are available only as oral preparations.

Both have good oral bioavailability. Both are highly protein bound. However, they differ in their metabolism.[54] Clonazepam is converted to inactive metabolites, whereas clobazam is metabolized in the liver to the active *N*-desmethylclobazam. Clobazam and its active metabolite have significantly greater binding affinity for $GABA_A$ α2 subunit, which mediates anticonvulsant effects without sedative actions.[55] Clonazepam has equal affinity for α1 and α2 subunits. The active metabolite of clobazam is subject to interaction with inhibitors of CYP2C19, which can result in its accumulation and associated sedation. These inhibitors include felbamate, cannabidiol, and cenobamate. Both clonazepam and clobazam have long half-lives, justifying once-daily dosing, although clobazam was dosed 2 times a day in clinical trials. Both clonazepam and clobazam are broad-spectrum agents, although their FDA indication is limited to generalized seizure types.

Drowsiness is a common adverse effect with these agents that improves over time. It is less likely with clobazam. With increasing doses, nystagmus, incoordination, unsteadiness, and dysarthria may occur. Tolerance may develop to the therapeutic effect of benzodiazepines, but this appears less likely with clobazam. Withdrawal seizures may occur with abrupt discontinuation. All benzodiazepines are controlled substances.

Place in Therapy

Both clonazepam and clobazam are typically used as adjunctive therapy and have limited data to support monotherapy use. The clobazam FDA indication is for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age or older. Class IV evidence of efficacy in adjunctive treatment of drug-resistant focal epilepsy and idiopathic generalized epilepsy has been reported.[56]

FELBAMATE

Felbamate was the first second-generation antiseizure medication approved in the United States in 1993. It has multiple mechanisms of action, including *N*-methyl-D-aspartate (NMDA) receptor antagonism, GABA enhancement, and sodium channel blocking. It is available as an oral preparation.

Felbamate has excellent oral bioavailability; its protein binding is not clinically significant. It is metabolized in the liver to inactive metabolites, with a half-life of 20 to 23 hours. It is an inhibitor of CYP2C19, CYP1A2, and β-oxidation, inhibiting the metabolism of phenobarbital, phenytoin, valproate, carbamazepine epoxide, *N*-desmethylclobazam, and warfarin, and it is a weak inducer of CYP3A4, decreasing carbamazepine levels and reducing oral contraceptive efficacy.

Felbamate is a broad-spectrum agent effective against focal seizures as well as generalized seizures in the setting of Lennox-Gastaut syndrome. The recommended starting dose is 600 mg 2 times a day, with subsequent titration by 600 mg/wk to 1200 mg/wk up to 1200 mg 3 times a day.

The most common possible adverse effect of felbamate is gastrointestinal irritation with anorexia, nausea, and vomiting, which can be helped by administration with food. Felbamate may also cause insomnia, irritability, headache, and weight loss. The most concerning toxicity is the potentially lethal aplastic anemia, with an estimated risk of 1 in 5000 to 1 in 8000 patients, and hepatic failure, with an estimated risk of 1 in 26,000 to 1 in 54,000 patients. Both are unlikely after 1 year of treatment, and aplastic anemia has not been reported in patients younger than 13 years. These two serious adverse effects have resulted in a boxed warning suggesting that felbamate should be used only for severe epilepsy in which treatment benefits outweigh the risks. It is recommended to check a complete blood cell count and liver function test before starting felbamate and to repeat the tests every 2 weeks in the first 6 months of treatment. The frequency of monitoring can be reduced to every 3 months after 1 year of treatment.

Place in Therapy

Although felbamate was approved for monotherapy, it is not indicated as a first-line treatment because of its potential serious idiosyncratic toxicity. Adjunctive therapy or alternative monotherapy can be considered when other appropriate and safer options have failed.

KEY POINTS

- Valproate has a broad spectrum of efficacy against all focal and generalized seizure types.
- Valproate has the highest rate of teratogenicity among antiseizure medications and should be avoided in female patients of childbearing potential.
- Ethosuximide is the drug of choice for typical absence seizures as the only seizure type. Although valproate is equally effective, it is associated with more cognitive adverse effects.
- Tolerance may develop to the therapeutic effect of benzodiazepines; this appears less likely with clobazam than clonazepam.

GABAPENTIN

Gabapentin binds to the α2δ subunit of Na_Vs, reducing the influx of calcium and associated neurotransmitter release under hyperexcitable conditions. It is available as an oral preparation only.

Gabapentin bioavailability is low and variable between subjects and even in the same subject. Because of its active saturable transport system from the gut, its bioavailability decreases with increasing doses, from 60% after a single dose of 300 mg to 29% for 1600 mg 3 times a day.[57] Protein binding is negligible. It is eliminated unchanged in the urine. Its half-life is 5 to 7 hours. It has no known interactions, other than potential antacid interference with its absorption.

Gabapentin is a narrow-spectrum agent against focal seizures. It may cause exacerbation of myoclonus.[58] It is also FDA approved for the treatment of postherpetic neuralgia. An extended-release preparation (gabapentin enacarbil) has been approved for the treatment of restless legs syndrome and postherpetic neuralgia, and another (gastroretentive dosage form) has been approved for the management of postherpetic neuralgia.

The recommended starting dose of gabapentin is 300 mg/d to 400 mg/d, to be increased by 300 mg to 400 mg every day up to 300 mg to 400 mg 3 times a day. The dose can be increased as needed up to 4800 mg/d in 3 divided doses.

Adverse effects may include drowsiness, dizziness, ataxia, tiredness, and weight gain. It may cause myoclonus.[59] It may cause cognitive slowing in older adults and emotional lability in children. Peripheral edema is more likely with increasing age. Gabapentin was reclassified as a controlled substance in some states.

Place in Therapy

Gabapentin can be used as adjunctive treatment for focal seizures. It is often chosen for its anecdotal benefit in the treatment of headache and other pain and its benefit for sleep. Although approved in Europe for initial monotherapy, a large randomized comparative trial found it less effective than lamotrigine.[18]

PREGABALIN

Pregabalin is structurally related to gabapentin and has a similar mechanism of action. It is also available only as an oral preparation. Unlike gabapentin, pregabalin has very good oral bioavailability, which is independent of dose. Like gabapentin, it has no protein binding and is not metabolized in humans, and it has no known interactions. It is excreted unchanged in the urine. Its half-life is about 6 hours.

Pregabalin is a narrow-spectrum drug against focal seizures. The official FDA epilepsy indication is adjunctive therapy for adult patients with focal-onset seizures. Like gabapentin, pregabalin has a narrow spectrum of efficacy against focal seizures and may exacerbate generalized myoclonic and absence seizures. It also has an FDA indication for neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and neuropathic pain associated with spinal cord injury. The starting dose is 75 mg 1 time (at bedtime) or 2 times a day. The dose can then be increased by 75 mg to 150 mg every week as needed, until seizure control, appearance of adverse effects, or reaching a maximum dose of 300 mg 2 times a day.

The possible adverse effects of pregabalin include dizziness, somnolence, increased appetite, weight gain, and peripheral edema. Myoclonus may occur with higher doses in some individuals. Pregabalin is a controlled substance.

Place in Therapy

Pregabalin is indicated as adjunctive therapy for focal seizures. It was inferior to lamotrigine as first-line therapy[60] and should probably not be used as a first-line treatment. However, a conversion-to-monotherapy study was successful.[61]

LAMOTRIGINE

Lamotrigine blocks sodium channels, like phenytoin and carbamazepine, but is thought to have other unrecognized actions to explain efficacy against absence seizures. It is available as an oral preparation only.

Lamotrigine has excellent oral bioavailability. Its protein binding is not clinically significant. It is extensively metabolized in the liver, predominantly by glucuronidation, and then eliminated in the urine. The half-life is about 24 hours in monotherapy, at least twice as long when used with valproate, and about half as long when used with an enzyme inducer. Estrogen and pregnancy increase lamotrigine clearance.

Lamotrigine is a broad-spectrum antiseizure medication, although its FDA indications are limited to focal seizures, generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. It is less effective against generalized absence seizures than valproate and ethosuximide.[51] It may be effective against myoclonic seizures in some patients but may exacerbate these seizures in others. Lamotrigine also has an FDA indication for maintenance treatment in bipolar I disorder.

Lamotrigine requires a very slow titration to avoid the development of rash. In monotherapy, it should be initiated with a total daily dose of 25 mg/d for 2 weeks, followed by 50 mg/d for 2 weeks, then 100 mg/d. The total daily dose can then be increased as needed by 100 mg every 2 weeks. The titration rate is half as fast with adjunctive valproic acid but can be twice as fast in the presence of an enzyme inducer and absence of valproic acid. A serum concentration is helpful to guide further titration if seizures are still not controlled at a total daily dose of 600 mg/d. The suggested therapeutic range is 2 μg/mL to 20 μg/mL.[62] The extended-release preparation allows once-daily dosing and reduces toxicity from peak levels. It may improve efficacy when used 2 times a day in patients who are drug resistant.[63]

Dose-related adverse effects may include dizziness, blurred vision, diplopia, unsteadiness, nausea and vomiting, headache, and tremor. A serum concentration is indicated for symptoms that could be consistent with lamotrigine toxicity, particularly if the baseline concentration is greater than 10 μg/mL.[64] Rash is seen in about 3% of patients, with a higher incidence in children, with coadministration of valproic acid, and with faster titration and higher doses. The risk of rash is increased in patients with a prior rash on carbamazepine or phenytoin.[65] Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome, and hemophagocytic lymphohistiocytosis are rare serious idiosyncratic adverse effects. A 2023 warning of cardiac rhythm and conduction abnormalities is based on in vitro findings and does not have definite clinical relevance.[66]

KEY POINTS

- Felbamate-related aplastic anemia and liver failure are unlikely to start after 1 year of treatment.
- Gabapentin bioavailability is low and decreases with increasing doses.
- Like gabapentin, pregabalin has a narrow spectrum of efficacy against focal seizures and may exacerbate generalized myoclonic and absence seizures.
- Lamotrigine clearance is decreased by valproate and increased by estrogen and pregnancy as well as by enzyme inducers.

Place in Therapy

Lamotrigine is an important first-line antiseizure medication for focal seizures and generalized tonic-clonic seizures. Several comparative trials have favored lamotrigine over other antiseizure medications for focal seizures in the balance of tolerability and efficacy.[18,21,67] However, it was inferior to valproic acid for idiopathic generalized epilepsy[49] and inferior to ethosuximide for generalized absence seizures.[51] Lamotrigine is less sedating and has fewer cognitive adverse effects than traditional antiseizure medications. Its monotherapy use is associated with one of the lowest rates of teratogenicity, favoring its use in female patients of childbearing age. Lamotrigine may have pharmacodynamic interactions with other classic sodium channel blockers, resulting in adverse effects at lower-than-expected serum concentrations. However, its combination with valproate can be synergistic, with greater efficacy than predicted.[68,69]

TOPIRAMATE

Topiramate has multiple mechanisms of action, including antagonism of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors, augmentation of GABA activity, and blocking of Na_Vs. It is also a weak carbonic anhydrase inhibitor, but this mechanism does not contribute significantly to its efficacy. It is available as an oral preparation.

Topiramate has excellent oral bioavailability. Its protein binding is not clinically significant. It is partially metabolized in the liver, with about 70% eliminated unchanged in the urine. Its half-life is approximately 21 hours. It is a mild inducer of CYP3A4, reducing the efficacy of the oral contraceptive at a dose equal to or greater than 200 mg/d, and a mild inhibitor of CYP2C19.

Topiramate is a broad-spectrum antiseizure medication effective against focal and generalized tonic-clonic seizures. A pilot trial suggested it is not effective for generalized absence seizures.[70] It is FDA approved for migraine prophylaxis and as a weight-loss preparation in combination with phentermine. It is also frequently used off-label for bipolar disorder. Topiramate has to be titrated gradually to manage cognitive adverse effects. It is suggested to start with 25 mg/d and increase the dose by 25 mg every week up to a total daily dose of 100 mg/d. Further titration by 25 mg to 50 mg every week can be considered, up to a total daily dose of 400 mg/d in 2 divided doses. Extended-release preparations with once-daily dosing may improve tolerability.

Topiramate is less well tolerated than lamotrigine, the main tolerability issue being the possible cognitive adverse effects, including cognitive slowing, decreased attention and memory, impaired executive function, word-finding difficulty, and reduced verbal fluency. Patients may not be aware of these cognitive difficulties.[71,72] Other possible adverse effects include sedation, fatigue, dizziness, ataxia, and depression. Kidney stones occur in about 1.5% of individuals. Decreased appetite and weight loss may also occur. Paresthesia in the hands and feet can occur with initiation and with dose increase but usually resolves. This effect is due to the carbonic anhydrase inhibition activity of this drug. Oligohidrosis, hyperthermia, and metabolic acidosis may occur, more commonly in children. Acute myopia and secondary angle-closure glaucoma are reported rarely. Hyperammonemia may occur when topiramate is used in conjunction with valproate. Topiramate exposure in utero is associated with low birth weight,[73] increased birth defects at a rate of approximately 4%, particularly

oral clefts,[74] and increased risk of autism spectrum disorder and intellectual disability.[75]

Place in Therapy

Although topiramate is FDA approved for initial monotherapy for focal seizures and generalized tonic-clonic seizures, it is not a drug of first choice because of its cognitive adverse effects, unless its use is justified by comorbidity, such as migraine or obesity. It is effective as adjunctive therapy for focal and generalized seizures in Lennox-Gastaut syndrome.

TIAGABINE

Tiagabine inhibits GABA reuptake at the synapse. It is available as an oral preparation only.

Tiagabine has excellent oral bioavailability. It is 96% protein bound, but this is of limited importance because dosing decisions are not dependent on the level, and its serum concentration is so low that it does not significantly compete for protein binding. It is extensively metabolized in the liver. Its half-life is 7 to 9 hours in monotherapy, shortened to 2 to 5 hours in the presence of an enzyme inducer.

Tiagabine has a narrow spectrum of efficacy against focal seizures only. It may exacerbate generalized absence and myoclonic seizures. It is used off-label in the management of spasticity in multiple sclerosis, in the treatment of addiction, and to increase deep sleep proportion. It should be started at 4 mg at bedtime and increased by 4 mg every week to an initial target dose of 8 mg 3 times a day. The dose can be increased further by 4 mg every week up to 12 mg to 16 mg 3 times a day. A higher dose may be used in the presence of an enzyme inducer.

The most common adverse effects are dizziness, asthenia, nervousness, tremor, depression, and emotional lability, which are more common during titration. Tiagabine may be associated with dose-related episodes of nonconvulsive status epilepticus or encephalopathy, which may occur even in the absence of epilepsy.[76,77]

Place in Therapy

Tiagabine should be reserved for use as adjunctive therapy for focal seizures.

LEVETIRACETAM

Levetiracetam's main mechanism of action is binding to the synaptic vesicle protein SV2A. This seems to result in nonspecific decrease in neurotransmitter release in a state of neuronal hyperactivation. Levetiracetam is available in oral and IV formulations.

Levetiracetam has excellent oral bioavailability and very low protein binding. It has no hepatic metabolism; 66% is excreted unchanged in the urine, and the rest is hydrolyzed to inactive compounds. The half-life is 6 to 8 hours. It has no known significant pharmacokinetic interactions.

Levetiracetam is a broad-spectrum drug, effective against focal seizures, generalized tonic-clonic seizures, and generalized myoclonic seizures. Levetiracetam is the only antiseizure medication with Class I evidence for efficacy against myoclonic seizures. It may be more effective than lamotrigine in girls and young women with juvenile myoclonic epilepsy, for whom valproate is not a recommended option.[78] It is best to start with 500 mg/d in 2 divided doses

or once at bedtime with the extended-release preparation. The dose can then be increased as needed and as tolerated up to a total daily dose of 3000 mg/d to 4000 mg/d. However, post hoc analysis from clinical trials indicates that efficacy is already maximal at the initial titration dose.[79] Therefore, upward dose adjustments should be limited when no added benefit is seen after one or two increments. Alternative therapy or adjunctive therapy should then be considered.

The most common possible adverse effects include somnolence, dizziness, and asthenia. Irritability and hostility may occur, more often in children. Depression, anxiety, and, rarely, psychosis may also occur.

Place in Therapy

Although levetiracetam is not FDA approved for monotherapy in the United States, it is used widely as a first-line treatment for focal and generalized tonic-clonic seizures and is approved for initial monotherapy in Europe. It is also an excellent adjunctive treatment in view of its safety and absence of interactions. The IV preparation has been used as a second-line agent in the treatment of status epilepticus.[80]

BRIVARACETAM

Brivaracetam is structurally related to levetiracetam and has a similar mechanism of action through binding to SV2A but with approximately 20-fold higher affinity and greater selectivity. It also has a higher brain permeability than levetiracetam. It is available in oral and IV formulations.

Brivaracetam has excellent bioavailability after oral administration. It is weakly bound to plasma proteins. Its half-life is approximately 7 to 8 hours. It is renally excreted after extensive metabolism, primarily by hydrolysis and to a lesser extent hydroxylation mainly via CYP2C19. Brivaracetam has more interactions than levetiracetam. Its clearance is increased by enzyme inducers. It may increase carbamazepine epoxide and may also increase phenytoin concentration by up to 20%.

Although brivaracetam has a broad spectrum of efficacy in preclinical models, human trials providing Class I evidence have only been conducted in patients with focal seizures.[81] However, open-label data support efficacy for generalized seizure types, particularly in patients with juvenile myoclonic epilepsy.[82] Pooled analyses demonstrated efficacy greater than placebo at 50 mg/d, 100 mg/d, and 200 mg/d administered in 2 divided doses as adjunctive therapy.[83] Post hoc analysis of pooled data showed that most (75% to 100%) responders responded from the time of treatment initiation.[84] The recommended starting dose is 50 mg 2 times a day, followed by adjustment based on response and tolerability, either down to 25 mg 2 times per day or up to 100 mg 2 times a day. However, it is reasonable to start at 25 mg 2 times a day in older patients or those at greater risk of adverse effects. The most commonly reported adverse experiences occurring more often than placebo were somnolence, dizziness, and fatigue. Irritability was reported only in 3.2% of patients receiving brivaracetam compared with 1.1% of those receiving placebo. Brivaracetam is a controlled substance.

Place in Therapy

Brivaracetam is FDA approved for the treatment of partial-onset seizures in patients 4 years of age and older. This indication includes monotherapy and

adjunctive use of the drug, although it has not specifically undergone initial monotherapy trials.

Brivaracetam is not effective when added to levetiracetam.[85] Open-label studies suggested that behavioral adverse effects from levetiracetam may improve after switching to brivaracetam.[86,87] As a result, one indication for using brivaracetam is in patients who are unable to tolerate levetiracetam due to behavioral adverse effects or deemed at risk of behavioral adverse effects from levetiracetam. The IV brivaracetam preparation has been explored in the treatment of status epilepticus because of its superior brain permeability.[88,89]

ZONISAMIDE

Zonisamide is structurally related to sulfonamides. It has multiple mechanisms of action, including blocking T-type calcium channels (predictive of efficacy against absence seizures), blocking sodium channels, and weak inhibition of carbonic anhydrase activity. It is available only as an oral preparation.

Zonisamide has excellent oral bioavailability. Protein binding is not clinically significant. It is metabolized in the liver to inactive metabolites. It has a long half-life of about 60 hours. It is not a hepatic enzyme inducer or inhibitor.

Zonisamide is considered a broad-spectrum antiseizure medication, although Class I trials have only been conducted in patients with focal seizures. The starting dose is 100 mg at bedtime for 2 weeks, then 200 mg at bedtime. The dose can be increased by 100 mg every 2 weeks as needed, up to 600 mg/d once at bedtime or in two divided doses. The suggested therapeutic range for plasma concentration is 10 μg/mL to 40 μg/mL

Possible adverse effects include sedation, ataxia, dizziness, nausea, fatigue, agitation, irritability, and anorexia. Weight loss may occur. Cognitive slowing and difficulty with concentration may be seen, particularly at higher doses, but are less pronounced than with topiramate. Rarely, depression and psychosis may occur. Serious rash, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, occurs rarely. Kidney stones occur in up to 4% of patients but may be prevented with adequate hydration. Oligohidrosis, hyperthermia, and metabolic acidosis occur rarely, more often in children.

Place in Therapy

Zonisamide is approved as initial monotherapy for focal seizures in Europe. In Japan, it is also approved as monotherapy for generalized seizures. The official FDA indication is for adjunctive therapy for focal seizures in adults. Zonisamide is rarely the first-choice agent for initial monotherapy because of its cognitive adverse effects. The large SANAD II randomized trial favored lamotrigine over zonisamide as first-line treatment for focal epilepsy.[67] However, zonisamide's long half-life could be an advantage, reducing the impact of a missed dose.

LACOSAMIDE

Lacosamide blocks sodium channels, enhancing slow inactivation, unlike most classic sodium channel blockers, which enhance fast sodium channel inactivation. It is available in oral as well as parenteral formulations.

Oral bioavailability is excellent. Protein binding is not clinically significant. Lacosamide is converted in the liver to inactive metabolites, but approximately

KEY POINTS

- Tiagabine may be associated with dose-related episodes of nonconvulsive status epilepticus or encephalopathy, even in subjects who do not have epilepsy.
- Levetiracetam is the only antiseizure medication with Class I evidence of efficacy against generalized myoclonic seizures.
- Brivaracetam may have fewer behavioral side effects than levetiracetam.

40% is eliminated unchanged in the urine. The half-life is approximately 13 hours.

Lacosamide is effective against focal-onset seizures as well as generalized-onset tonic-clonic seizures. It is not usually effective against generalized absence or myoclonic seizures, but it is unlikely to exacerbate these seizures in the majority of patients.[90] The starting dose is 100 mg/d (once at bedtime or in 2 divided doses) for 1 week, then 100 mg 2 times a day. The dose can then be titrated as needed by 100 mg every 1 to 2 weeks until seizures are controlled, side effects appear, or a total daily dose of 600 mg/d is reached.

The most common possible adverse effects include dizziness, nausea, vomiting, diplopia, fatigue, and sedation, all of which are more common at higher doses. These adverse effects are also more likely when lacosamide is used in conjunction with other sodium channel blockers.[91] Lacosamide may produce a dose-dependent prolongation in PR interval, which could be clinically significant in patients with known cardiac conduction problems, or if it is combined with other drugs that have a similar effect. Lacosamide is a controlled substance.

Place in Therapy

Lacosamide is indicated as monotherapy or adjunctive therapy for focal seizures and as adjunctive therapy in the treatment of generalized tonic-clonic seizures in patients 4 years of age or older. Its favorable pharmacokinetic profile and rapid titration make it a suitable first-line agent for focal epilepsy. The parenteral formulation is indicated as short-term replacement when oral administration is not feasible in patients taking oral lacosamide; it is effective against nonconvulsive seizures in critically ill patients.[92] Several reports support efficacy in status epilepticus.[93,94] When lacosamide is used as adjunctive therapy, it may have greater efficacy and better tolerability if it is combined with a non–sodium channel blocking drug.[91]

VIGABATRIN

Vigabatrin is an irreversible inhibitor of GABA transaminase, resulting in accumulation of GABA. It is available as an oral formulation. Vigabatrin has excellent oral bioavailability and no protein binding. It is not significantly metabolized and is eliminated unchanged in the urine. The half-life is 10.5 hours in young adults and 5 to 6 hours in infants. However, its duration of action outlasts its presence in serum. Vigabatrin is a weak inducer of CYP2C9.

Vigabatrin is a narrow-spectrum drug effective against focal seizures. It may worsen absence and myoclonic seizures in idiopathic generalized epilepsy.[95] However, it is effective against infantile spasms, particularly in the presence of tuberous sclerosis.[96] The starting adult dose is 500 mg 2 times a day, then it is titrated by 500 mg/wk up to 1.5 g 2 times a day. The dose can be increased further, as needed, up to 3 g 2 times a day, but this increases the risk of adverse effects with a low chance of additional therapeutic benefit.

Common vigabatrin adverse effects include sedation, fatigue, dizziness, and ataxia. Irritability, behavior changes, psychosis, and depression may also be observed. Weight gain may occur. The most concerning possible adverse effect is a progressive and permanent bilateral concentric visual field constriction, which may occur in up to 30% to 40% of individuals.[97] The risk increases with increased daily dose and increased duration of therapy.[98]

Place in Therapy

Vigabatrin use is reserved for adjunctive therapy in patients who have not had favorable responses to several alternative treatments, and monotherapy in infants with infantile spasms. Because of the visual toxicity, periodic visual assessment is recommended at baseline and every 3 months, and treatment should be continued only if considerable benefit is observed in the first 3 months.

RUFINAMIDE

Rufinamide is a sodium channel blocker, although additional mechanisms of action are likely. It is available only as an oral preparation. Oral bioavailability is very good with food but is decreased in the absence of food. Protein binding is not clinically significant. It is metabolized by enzymatic hydrolysis to an inactive metabolite eliminated in the urine. The half-life is approximately 6 to 10 hours. It is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 and uridine diphosphate glucuronyltransferase. The addition of valproate decreases rufinamide clearance and increases rufinamide levels by up to 70%.

Rufinamide is a broad-spectrum antiseizure medication, but its efficacy against focal seizures was not sufficient for an FDA indication. The starting dose is 400 mg/d, after which it is increased by 400 mg every other day until seizure control or until a total daily dose of 3200 mg is reached (in 2 divided doses).

The possible adverse effects of rufinamide include dizziness, fatigue, somnolence, and headache. Vomiting may occur in children. Rufinamide may cause a shortening of the QT interval.

Place in Therapy

Rufinamide is FDA indicated as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in pediatric patients 1 year of age and older and in adults.

PERAMPANEL

Perampanel is a selective noncompetitive AMPA glutamate receptor antagonist. It is available as an oral preparation. It has excellent oral bioavailability and is 95% protein bound. It is extensively metabolized in the liver. It has a long half-life of about 105 hours. At a dose of 12 mg (not 8 mg), it accelerates the metabolism of levonorgestrel, a progesterone component of the oral contraceptive pill. Perampanel is effective for focal seizures and generalized tonic-clonic seizures.[99] Anecdotal evidence supports efficacy against myoclonic and absence seizures.[100] The starting dose is 2 mg/d for 1 to 3 weeks, then 4 mg/d. The dose can be increased further by 2 mg every 3 weeks as needed, up to 8 mg/d in monotherapy and 12 mg/d when used with an enzyme-inducing agent.

The possible adverse effects of perampanel include dizziness, somnolence, headache, fatigue, ataxia, and blurred vision. Aggression and hostility may occur, with an estimated incidence of about 20% at a dose of 12 mg/d, resulting in a boxed warning.[101] Behavioral changes were more common in patients with intellectual disability.[102] Perampanel is a controlled substance.

Place in Therapy

Perampanel is indicated for focal seizures (adjunctive and monotherapy) and as adjunctive treatment for generalized tonic-clonic seizures. Its long half-life may

KEY POINTS

- Zonisamide's long half-life of about 60 hours may be an advantage in reducing the impact of a missed dose.
- Lacosamide may produce a dose-dependent prolongation in PR interval, which could be clinically significant in patients with known cardiac conduction problems, or if it is combined with other drugs that have a similar effect.
- Long-term vigabatrin use may be associated with irreversible visual field constriction; hence, it should only be continued if it produces a remarkable improvement in seizure control.
- Valproate reduces rufinamide clearance; as a result, rufinamide has to be started at a lower dose and titrated more slowly in the presence of valproate.

be an advantage, with two studies showing its use to be associated with a reduction in health care resource utilization, including hospitalizations and outpatient visits.[103,104] Its long half-life reduces the impact of a missed dose and allows abrupt discontinuation, without the need for taper.[105] Although there is no FDA indication for myoclonic seizures, several case reports and case series suggest particular efficacy in progressive myoclonic epilepsies, which are usually resistant to therapy.[106-109] There have been several reports of successful use of perampanel in the treatment of refractory and super-refractory status epilepticus.[110] An IV formulation is under investigation for replacement therapy.[111]

CANNABIDIOL

Cannabidiol was first marketed in the United States in November 2018. It is a cannabinoid but does not interact with the cannabinoid receptor CB1 and does not share the psychoactive properties of tetrahydrocannabinol. Its exact mechanisms of action are not known, but it may enhance GABA activity through allosteric modulation of the $GABA_A$ receptor and enhancement of currents elicited by low GABA concentrations. It may also play a role in modulation of intracellular calcium. Its bioavailability is increased by administration with a high-fat meal. It is highly protein bound (>94%). Cannabidiol is metabolized in the liver, primarily by CYP2C19 and CYP3A4 enzymes, and converted to an active then inactive metabolite. Its clearance is increased by inducers and decreased by inhibitors of CYP2C19 and CYP3A4. It interacts with several antiseizure medications, most notably with clobazam, increasing the concentration of its active metabolite *N*-desmethylclobazam.[112] Cannabidiol is available only as an oral solution. The recommended starting dose is 5 mg/kg/d in 2 divided doses for 1 week, then 10 mg/kg/d in 2 divided doses. Its most common possible adverse effects are sedation, fatigue, decreased appetite, and diarrhea. It may produce an increase in liver enzymes, particularly when used in conjunction with valproate or with valproate and clobazam. Liver enzymes and total bilirubin levels should be obtained before treatment and at 1, 3, and 6 months after initiation of treatment.

Place in Therapy

Cannabidiol is FDA indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older, based on blinded controlled trials.[113-116] Open-label trials also suggest efficacy for other forms of epilepsy.[117-121] Artisanal cannabidiol formulations are used without prescription by many patients with epilepsy in the United States, but their efficacy has not been evaluated in these settings.

STIRIPENTOL

Stiripentol was FDA approved for the treatment of seizures associated with Dravet syndrome in patients 2 years or older also taking clobazam. Its mechanism of action may involve both direct allosteric modulation of $GABA_A$ receptors, preventing GABA reuptake, and inhibition of CYP enzyme activity resulting in increased concentration of clobazam and its active metabolite. It has good bioavailability and is 99% protein bound. The half-life is dose-dependent, longer with increasing dose in adult volunteers; the half-life also increased with

increasing weight in children with Dravet syndrome. Stiripentol is an inhibitor of several liver enzymes, namely CYP2C9 and CYP2C19. Its addition causes elevation of *N*-desmethylclobazam, the active metabolite of clobazam, and to a lesser extent clobazam. It may also increase the concentration of valproate, so that a reduction in clobazam and valproate doses is recommended on initiation. The recommended dose is 50 mg/kg/d administered in 2 or 3 divided doses, not to exceed a total daily dose of 3000 mg/d. The most common adverse experiences occurring more frequently than with placebo are somnolence, anorexia, nausea, and weight loss.

Place in Therapy

Stiripentol is currently indicated only for the adjunctive treatment of patients with Dravet syndrome also taking clobazam; clinicians should keep in mind the need for adjusting concomitant medications because of a high propensity for interactions.

CENOBAMATE

Cenobamate is an alkyl-carbamate with two mechanisms of action: blocking the sodium channel, preferentially attenuating the persistent sodium current, and enhancing GABA activity through positive allosteric modulation of the $GABA_A$ receptor. Cenobamate has very good oral bioavailability of approximately 88%. Its protein binding of 60% is not clinically relevant. It is extensively metabolized by glucuronidation and oxidation. It is excreted predominantly as inactive metabolites in the urine. Its half-life is 50 to 60 hours, justifying once-daily dosing. It has several important interactions. Its concentration is reduced by enzyme inducers. It is an inhibitor of CYP2C19, reducing the clearance of phenytoin, phenobarbital, and the active metabolite of clobazam. However, it induces CYP3A4, which may reduce the efficacy of oral contraceptives. It may also reduce lamotrigine concentration. The most common possible adverse effects were somnolence, dizziness, and fatigue.[122] It did not seem to adversely affect cognition, affect, or quality of life.[123,124] DRESS (**d**rug **r**ash with **e**osinophilia and **s**ystemic **s**ymptoms) syndrome, which occurred rarely in early studies, did not recur in a large safety study with a slowed titration rate.[125] The starting dose is 12.5 mg/d for 2 weeks, 25 mg/d for 2 weeks, 50 mg/d for 2 weeks, and then 100 mg/d, which is the lowest dose proven effective in one clinical trial.[126] After that, the dose can be increased as needed by 50 mg every 2 weeks, up to 400 mg/d. Cenobamate is a controlled substance.

Place in Therapy

Cenobamate was FDA approved for the treatment of focal-onset seizures in adults in November 2019 and was marketed as of May 2020. Its efficacy as adjunctive therapy was exceptional, with higher seizure-free rates than reported with any other antiseizure medication in the past 30 years.[126,127] This supports its early use in patients with drug-resistant epilepsy, as its safety is confirmed with accumulated experience.

FENFLURAMINE

Fenfluramine is a repurposed medication, originally launched as an appetite suppressant in the early 1970s and used predominantly in combination with phentermine. It was eventually withdrawn because of reports of heart valve

KEY POINTS

- **Perampanel has a very long half-life, justifying once-daily dosing.**
- **Cannabidiol reduces clearance of the active metabolite of clobazam, requiring reduction in the clobazam dose.**

abnormalities and pulmonary hypertension. However, observations of benefits in patients with epilepsy resulted in its reevaluation as an antiseizure medication. It acts to increase serotonin by disrupting its vesicular storage and reversing serotonin transporter function. Additionally, its active metabolite binds to and activates serotonin receptors. It is converted to the active metabolite norfenfluramine, which is then converted to inactive metabolites. Its half-life is approximately 20 hours. It does have important interactions. In particular, coadministration with stiripentol and clobazam increases its plasma concentration. The recommended starting dose is 0.1 mg/kg 2 times a day. The main possible adverse effects are decreased appetite, fatigue, somnolence, and weight decrease.[128,129] Valvular disease or pulmonary hypertension has not been observed in pediatric epilepsy studies, possibly because lower doses were used than for appetite suppression and because of the younger age of epilepsy patients compared with those treated for obesity in the past. Fenfluramine is a controlled substance.

Place in Therapy

Fenfluramine is currently approved for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients 2 years of age and older.

GANAXOLONE

Ganaxolone is a neuroactive steroid that is a positive allosteric modulator of $GABA_A$ receptors, targeting a unique binding site distinct from benzodiazepines or barbiturates. Its oral bioavailability is low but markedly enhanced when administered with a high-fat meal. It is highly protein bound (approximately 99%). It is extensively metabolized by CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6 in the liver. Its half-life is approximately 34 hours. It is not an enzyme inducer or inhibitor. However, its clearance is increased by enzyme inducers. The most common treatment-related adverse effect is somnolence or sedation.[130]

Place in Therapy

Ganaxolone is currently indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder in patients 2 years of age and older.

MEDICAL TREATMENT OF EPILEPSY AFTER FAILURE OF THE FIRST ANTISEIZURE MEDICATION

If the first appropriate, tolerated, and optimally dosed antiseizure medication fails to control seizures, pseudoresistance must be ruled out before considering the next step.

Establishing True Failure of Efficacy

If the first antiseizure medication fails because of a lack of efficacy, it is important to consider the possibilities of apparent medication failure due to poor adherence, nonepileptic events, incorrect epilepsy diagnosis, inappropriate antiseizure medication choice, or poor compliance with lifestyle requirements (eg, sleep deprivation or heavy episodic drinking). Compliance with lifestyle requirements is most problematic in patients with idiopathic generalized epilepsy.[131] The presence of focal features or focal evolution in generalized-onset

seizures may lead to an incorrect diagnosis of focal epilepsy and administration of narrow-spectrum antiseizure medications inappropriate for generalized epilepsy.[132,133] The possibility that an insufficient antiseizure medication dose is used should also be considered, and a serum concentration may help explore how much flexibility there is in dosing. For example, lamotrigine is indicated at a dose up to 500 mg/d, which usually has a corresponding serum concentration less than 10 μg/mL, but in clinical practice, seizure freedom was reported with higher doses and serum concentrations between 10 μg/mL and 20 μg/mL.[62]

Choosing the Next Antiseizure Medication

Regardless of whether the first antiseizure medication failed because of a lack of efficacy or tolerability, the next antiseizure medication to be considered must be effective against the patient's seizure types. Almost all antiseizure medications except ethosuximide are effective against focal seizures, but a smaller number of antiseizure medications are effective against generalized onset seizures. If the classification of seizures is not certain, a broad-spectrum agent is preferred. In that situation, narrow-spectrum agents such as gabapentin, oxcarbazepine, and related agents, which may precipitate myoclonic seizures, should be avoided.[134] If a patient has multiple seizure types that cannot be addressed with a single antiseizure medication, then the most disabling seizures should be addressed.[134] The second antiseizure medication must have a good safety profile and no adverse effects related to the patient's comorbidities. For example, levetiracetam, topiramate, zonisamide, and perampanel may not be ideal for a patient with bipolar disorder or depression. The chosen antiseizure medication should also be effective against a patient's comorbidities. For example, topiramate may be a good choice in an individual with frequent migraine headaches, and lamotrigine could be a mood stabilizer in the presence of bipolar I disorder.

Other considerations in the antiseizure medication choice include the need for titration. An antiseizure medication with a slow titration rate may not be appropriate if there is an urgent need to control severe or frequent seizures. Other individual considerations apply, just as in choosing the first antiseizure medication. Antiseizure medications that reduce the efficacy of oral contraceptives and antiseizure medications with known teratogenicity, such as valproate and topiramate, may not be the most appropriate choices in many people with epilepsy of childbearing potential. A patient with adherence challenges may benefit from an antiseizure medication with a long half-life that can be taken once daily and can be forgiving in the event of missed doses. In contrast, missing doses of carbamazepine or oxcarbazepine can precipitate severe rebound seizures.[29]

Antiseizure Medication Failure Due to Intolerability

If the first antiseizure medication fails because of a lack of tolerability, it should be replaced with an alternative monotherapy. The same is true if the medication fails because of a lack of both tolerability and efficacy, unless the lack of tolerability was dose related. The next antiseizure medication should not be associated with the same adverse effect that caused the intolerability. An expert consensus statement recommended that an antiseizure medication with a different mechanism of action is preferable.[134] However, if the first antiseizure medication was effective, it could be argued that an antiseizure medication with the same mechanism and lower likelihood of causing the adverse effect would be

KEY POINTS

- **Cenobamate requires a very slow titration to avoid allergic skin reactions.**
- **Fenfluramine and its active metabolite act via serotonergic mechanisms.**
- **Ganaxolone is a neuroactive steroid indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder.**
- **Sleep deprivation and other lifestyle factors are common causes of apparent medication failure in idiopathic generalized epilepsy.**

a good choice. For example, if levetiracetam controls seizures but fails because of behavioral adverse effects, brivaracetam may be an appropriate replacement. Improvement or resolution of behavioral adverse effects was reported in the majority of patients who switched from levetiracetam to brivaracetam.[87]

Antiseizure Medication Failure Due to Lack of Efficacy

If the first antiseizure medication fails because of a confirmed lack of efficacy, the options of replacement monotherapy or adjunctive therapy seem to be equally effective.[135,136] Substitution monotherapy is favored when the first antiseizure medication was also not well tolerated or was totally ineffective. Substitution monotherapy would also be preferable in older adults who already take other medications, in people with epilepsy of childbearing potential contemplating pregnancy, in patients with adherence challenges, and when financial restrictions exist. If substitution monotherapy is chosen, a period of combination therapy is usually needed until the new antiseizure medication has reached an effective dose and is proven to be tolerated. At that point, the first antiseizure medication can be withdrawn gradually. There are a few exceptions to this rule when a switch can be made overnight. These include switching between medications in the same family, such as carbamazepine, oxcarbazepine, and eslicarbazepine acetate; gabapentin and pregabalin; or levetiracetam and brivaracetam. One study suggested the feasibility of an overnight switch from sodium channel blockers phenytoin, carbamazepine, or oxcarbazepine to lacosamide.[137] However, a study based on expert opinion recommended that the second monotherapy agent should have a different mechanism.[134]

Add-on therapy is preferred if the first antiseizure medication was well tolerated and partially effective or if the projected add-on agent has not been tested in monotherapy. Add-on therapy is also a good option if the first medication was partially effective and well-tolerated until a high dose was reached. In that case, the dose of the first medication can be reduced on addition of the second medication. A recent longitudinal study showed a trend for increased use of combination therapy relative to alternative monotherapy after failure of the first antiseizure medication, in the epoch of 2005 to 2015 compared with previous epochs.[135] The add-on therapy should not have negative pharmacokinetic interactions with the first antiseizure medication or other concomitant medications.[138] The use of an enzyme inducer with an antiseizure medication whose metabolism can be induced will reduce its efficacy. For example, perampanel efficacy was reduced when used with an enzyme inducer.[139] Enzyme inhibition is less of a problem as long as dosing accommodations are made. Evidence exists that combining two antiseizure medications with different mechanisms of action is associated with a greater balance of tolerability and efficacy.[140] In the large Glasgow cohort, a combination of a sodium channel blocker and levetiracetam had a better chance of achieving seizure freedom than pooled alternative combinations.[135] Combinations of brivaracetam with a sodium channel blocker were associated with a greater response rate than other brivaracetam combinations.[141] Another favorable combination includes an antiseizure medication with multiple mechanisms.[142] Combining medications with similar mechanisms may be associated with increased adverse effects as well as decreased efficacy. In particular, the combination of two sodium channel blockers may be associated with adverse effects while serum concentrations are in the therapeutic range because of

pharmacodynamic interactions. For example, lacosamide efficacy and tolerability were inferior when it was combined with another sodium channel blocking antiseizure medication compared with it in combination with a non–sodium channel blocking antiseizure medication.[91] In another notable example, brivaracetam was not effective when it was combined with levetiracetam.

When using antiseizure medication combinations, there should be a low threshold to reduce the dose of the first antiseizure medication if adverse effects emerge. Nonspecific adverse effects such as fatigue and sedation may be related to the total drug load and could be mitigated by reducing the dose of the first antiseizure medication that failed to control seizures on its own.

Synergistic Antiseizure Medication Combinations

Several medication combinations seem to have synergistic efficacy in animal models.[143] The ideal antiseizure medication combination has supra-additive efficacy and infra-additive toxicity. Few combinations have been demonstrated to be synergistic in humans, but the combination of lamotrigine and valproate has the strongest evidence supporting its use.[70,144] Other potentially favorable combinations include lamotrigine and levetiracetam,[145,146] cannabidiol and clobazam,[147] lamotrigine and topiramate,[148] and cenobamate and clobazam.[149]

Optimizing Pharmacologic Management in Drug-resistant Epilepsy

Although there is a decreasing chance of seizure freedom with every medication failed,[150] prolonged seizure remissions are reported in up to one-quarter of patients with additional antiseizure medication introductions.[151] Because there is great variability among individuals in the dose-to-plasma concentration relationship, antiseizure medication plasma concentrations help determine if an insufficient antiseizure medication dose was used.[152]

Dose optimization may be particularly effective for several drugs acting on the sodium channel, such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine, and lacosamide. Most antiseizure medications have a suggested reference therapeutic range. However, the antiseizure medication plasma concentration necessary for seizure control varies greatly among individuals. Some patients achieve seizure freedom at concentrations less than the suggested reference range, whereas others may require a concentration greater than that range, without toxic adverse effects. A couple of separate "individual therapeutic concentrations" obtained a few months apart during the best sustained seizure control can serve as a reference therapeutic range for a patient. One antiseizure medication, carbamazepine, has evidence of improved efficacy as well as improved tolerability with the use of an extended-release preparation administered 2 times a day.[11] There is also one report of improved seizure control in patients with persistent seizures whose treatment was converted from immediate-release to extended-release lamotrigine administered 2 times a day.[63] Use of the extended-release preparation administered 2 times a day is expected to produce a more stable plasma concentration, reducing trough levels associated with lowering the seizure threshold and peak concentration associated with toxic adverse effects.

In two-drug combinations, an antiseizure medication that is ineffective should be replaced by a new one. It is preferable to avoid a three-drug combination, which increases the risk of pharmacokinetic and pharmacodynamic interactions. However, it may be unavoidable when each antiseizure medication in a

KEY POINTS

- When the first antiseizure medication fails because of adverse effects, the replacement antiseizure medication should not be associated with the same adverse effects.
- If the first antiseizure medication fails because of a confirmed lack of efficacy, replacement monotherapy and adjunctive therapy are equally effective alternatives.
- Substitution monotherapy usually requires a period of combination therapy until an effective dose of the new antiseizure medication is reached and is proven to be tolerated.
- Adjunctive therapy may be preferred if the first antiseizure medication was partially effective and well tolerated.
- Antiseizure medication combinations with different mechanisms of action may have a greater probability of success.
- Dose optimization may be particularly effective for several medications acting on the sodium channel.
- In drug combinations, an antiseizure medication that is ineffective should be replaced to avoid polypharmacy.

combination has had partial efficacy. The more recently introduced antiseizure medication cenobamate has demonstrated exceptional rates of seizure freedom for patients with drug-resistant epilepsy and may be considered before surgery for patients who are not ideal surgical candidates.[127]

CONCLUSION

In conclusion, many antiseizure medications are available for the treatment of epilepsy, with specific advantages and disadvantages. Some antiseizure medications have additional efficacy in the treatment of comorbidities such as migraine or bipolar disorder. Considerations in antiseizure medication choice include the antiseizure medication's efficacy profile as well as patient-specific factors. Antiseizure medication combinations should avoid unfavorable pharmacokinetic and pharmacodynamic interactions.

The most notable developments since the last version of this article are the FDA approval of one new antiseizure medication, ganaxolone, with a very narrow indication, and expansion of the indications of some antiseizure medications, particularly the approval of cannabidiol for tuberous sclerosis. There has also been increasing awareness of autoimmune pathophysiology underlying epilepsy in many patients, usually requiring immunotherapy for optimal management. Improved understanding of the underlying pathophysiology of epilepsy in individual patients will allow more specific antiseizure medication therapy in the future.

REFERENCES

1 Cohen JM, Alvestad S, Cesta CE, et al. Comparative safety of antiseizure medication monotherapy for major malformations. Annals of Neurology 2023;93:551-562.

2 Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurology 2018;17:530-538.

3 Tomson T, Battino D, Bromley R. Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. Epileptic Disord 2019; 21(6):497-517. doi:10.1684/epd.2019.1105

4 Trinka E. Phenobarbital in status epilepticus - rediscovery of an effective drug. Epilepsy Behav 2023;141:109104. doi:10.1016/j.yebeh.2023.109104

5 Vajda FJE, Eadie MJ. The clinical pharmacology of traditional antiepileptic drugs. Epileptic Disord 2014;16(4):395-408. doi:10.1684/epd.2014.0704

6 Ding D, Zhang Q, Zhou D, et al. Cognitive and mood effects of phenobarbital treatment in people with epilepsy in rural China: a prospective study. J Neurol Neurosurg Psychiatry 2012;83(12): 1139-1144. doi:10.1136/jnnp-2012-303042

7 Hopfner F, Deuschl G. Managing essential tremor. Neurotherapeutics 2020;17(4):1603-1621. doi:10.1007/s13311-020-00899-2

8 Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med 1985;313(3):145-151. doi:10.1056/NEJM198507183130303

9 Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 2007; 68(20):1701-1709. doi:10.1212/01.wnl.0000261917.83337.db

10 Canger R, Altamura AC, Belvedere O, et al. Conventional vs controlled-release carbamazepine: a multicentre, double-blind, cross-over study. Acta Neurol Scand 1990;82(1): 9-13. doi:10.1111/j.1600-0404.1990.tb01579.x

11 Ficker DM, Privitera M, Krauss G, et al. Improved tolerability and efficacy in epilepsy patients with extended-release carbamazepine. Neurology 2005;65(4):593-595. doi:10.1212/01.wnl.0000172932.95985.51

12 Meador KJ, Loring DW, Ray PG, et al. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. Neurology 2001; 56(9):1177-1182. doi:10.1212/wnl.56.9.1177

13 Malow BA, Blaxton TA, Stertz B, Theodore WH. Carbamazepine withdrawal: effects of taper rate on seizure frequency. Neurology 1993;43(11): 2280-2284. doi:10.1212/wnl.43.11.2280

14 Marciani MG, Gotman J, Andermann F, Olivier A. Patterns of seizure activation after withdrawal of antiepileptic medication. Neurology 1985;35(11): 1537-1543. doi:10.1212/wnl.35.11.1537

15 Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res 1999;37(1):81-87. doi:10.1016/s0920-1211(99)00039-x

16 Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/ Carbamazepine Monotherapy Trial Group. Lancet 1995;345(8948):476-479. doi:10.1016/ s0140-6736(95)90581-2

17 Dam M, Ekberg R, Løyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. Epilepsy Res 1989;3(1):70-76. doi:10.1016/0920-1211(89)90070-3

18 Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007;369(9566):1000-1015. doi:10.1016/S0140-6736(07)60460-7

19 Reinikainen KJ, Keranen T, Halonen T, Komulainen H, Riekkinen PJ. Comparison of oxcarbazepine and carbamazepine: a double-blind study. Epilepsy Res 1987;1(5):284-289. doi:10.1016/0920-1211(87)90003-9

20 Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. Epilepsy Res 1996;23(2):149-155. doi:10.1016/0920-1211(95)00085-2

21 Rowan AJ, Ramsay RE, Collins JF, et al. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology 2005;64(11):1868-1873. doi:10.1212/01.WNL.0000167384.68207.3E

22 Baulac M, Patten A, Giorgi L. Long-term safety and efficacy of zonisamide versus carbamazepine monotherapy for treatment of partial seizures in adults with newly diagnosed epilepsy: results of a phase III, randomized, double-blind study. Epilepsia 2014;55(10): 1534-1543. doi:10.1111/epi.12749

23 Baulac M, Rosenow F, Toledo M, et al. Efficacy, safety, and tolerability of lacosamide monotherapy versus controlled-release carbamazepine in patients with newly diagnosed epilepsy: a phase 3, randomised, double-blind, non-inferiority trial. Lancet Neurol 2017;16(1): 43-54. doi:10.1016/S1474-4422(16)30292-7

24 Brodie MJ, Perucca E, Ryvlin P, et al. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. Neurology 2007;68(6):402-408. doi:10.1212/01.wnl.0000252941.50833.4a

25 Saetre E, Perucca E, Isojärvi J, Gjerstad L, LAM 40089 Study Group. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. Epilepsia 2007; 48(7):1292-1302. doi:10.1111/j.1528-1167.2007.01128.x

26 Trinka E, Ben-Menachem E, Kowacs PA, et al. Efficacy and safety of eslicarbazepine acetate versus controlled-release carbamazepine monotherapy in newly diagnosed epilepsy: a phase III double-blind, randomized, parallel-group, multicenter study. Epilepsia 2018;59(2): 479-491. doi:10.1111/epi.13993

27 Intravooth T, Staack AM, Juerges K, Stockinger J, Steinhoff BJ. Antiepileptic drugs-induced hyponatremia: review and analysis of 560 hospitalized patients. Epilepsy Res 2018;143:7-10. doi:10.1016/j.eplepsyres.2018.03.023

28 Berghuis B, van der Palen J, de Haan GJ, et al. Carbamazepine- and oxcarbazepine-induced hyponatremia in people with epilepsy. Epilepsia 2017;58(7):1227-1233. doi:10.1111/epi.13777

29 Azar NJ, Wright AT, Wang L, Song Y, Abou-Khalil BW. Generalized tonic-clonic seizures after acute oxcarbazepine withdrawal. Neurology 2008;70(22 Pt 2):2187-2188. doi:10.1212/01.wnl.0000313152.89906.5a

30 Koch MW, Polman SK. Oxcarbazepine versus carbamazepine monotherapy for partial onset seizures. Cochrane Database Syst Rev 2009;(4): CD006453. doi:10.1002/14651858.CD006453.pub2

31 Nevitt SJ, Tudur Smith C, Marson AG. Oxcarbazepine versus phenytoin monotherapy for epilepsy: an individual participant data review. Cochrane Database Syst Rev 2018; 2018(10):CD003615. doi:10.1002/14651858.CD003615.pub4

32 Hebeisen S, Pires N, Loureiro AI, et al. Eslicarbazepine and the enhancement of slow inactivation of voltage-gated sodium channels: a comparison with carbamazepine, oxcarbazepine and lacosamide. Neuropharmacology 2015;89: 122-135. doi:10.1016/j.neuropharm.2014.09.008

33 Holtkamp D, Opitz T, Hebeisen S, Soares-da-Silva P, Beck H. Effects of eslicarbazepine on slow inactivation processes of sodium channels in dentate gyrus granule cells. Epilepsia 2018;59(8): 1492-1506. doi:10.1111/epi.14504

34 Nunes T, Rocha JF, Falcão A, Almeida L, Soares-da-Silva P. Steady-state plasma and cerebrospinal fluid pharmacokinetics and tolerability of eslicarbazepine acetate and oxcarbazepine in healthy volunteers. Epilepsia 2013;54(1):108-116. doi:10.1111/j.1528-1167.2012.03595.x

35 Sperling MR, Harvey J, Grinnell T, et al. Efficacy and safety of conversion to monotherapy with eslicarbazepine acetate in adults with uncontrolled partial-onset seizures: a randomized historical-control phase III study based in North America. Epilepsia 2015;56(4): 546-555. doi:10.1111/epi.12934

36 Trinka E, Rocamora R, Chaves J, et al. Long-term efficacy and safety of eslicarbazepine acetate monotherapy for adults with newly diagnosed focal epilepsy: an open-label extension study. Epilepsia 2020;61(10):2129-2141. doi:10.1111/epi.16666

37 Meador KJ, Seliger J, Boyd A, et al. Comparative neuropsychological effects of carbamazepine and eslicarbazepine acetate. Epilepsy Behav 2019;94:151-157. doi:10.1016/j.yebeh.2019.02.034

38 Hirsch M, Immisch I, Knake S, Schulze-Bonhage A. A prospective longitudinal study of the effects of eslicarbazepine acetate treatment on bone density and metabolism in patients with focal-onset epilepsy. CNS Drugs 2023;37(11):973-980. doi:10.1007/s40263-023-01045-0

39 Abou-Khalil B, Klein P, Shah A, et al. Tolerability of adjunctive eslicarbazepine acetate according to concomitant lamotrigine or carbamazepine use: a subgroup analysis of three phase III trials in adults with focal (partial-onset) seizures. Epilepsy Res 2018;147:80-86. doi:10.1016/j.eplepsyres.2018.08.011

40 Pierre-Louis SJC, Brannegan RT, Evans AT. Seizure control and side-effect profile after switching adult epileptic patients from standard to extended-release divalproex sodium. Clin Neurol Neurosurg 2009;111(5):437-441. doi:10.1016/j.clineuro.2008.12.009

41 Smith MC, Centorrino F, Welge JA, Collins MA. Clinical comparison of extended-release divalproex versus delayed-release divalproex: pooled data analyses from nine trials. Epilepsy Behav 2004;5(5):746-751. doi:10.1016/j.yebeh.2004.07.007

42 Belcastro V, D'Egidio C, Striano P, Verrotti A. Metabolic and endocrine effects of valproic acid chronic treatment. Epilepsy Res 2013;107(1-2):1-8. doi:10.1016/j.eplepsyres.2013.08.016

43 Verrotti A, Mencaroni E, Cofini M, et al. Valproic acid metabolism and its consequences on sexual functions. Curr Drug Metab 2016;17(6):573-581. doi:10.2174/1389200217666160322143504

44 Tomson T, Battino D, Bonizzoni E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology 2015;85(10):866-872. doi:10.1212/WNL.0000000000001772

45 Christensen J, Grønborg TK, Sørensen MJ, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 2013;309(16):1696-1703. doi:10.1001/jama.2013.2270

46 Cohen MJ, Meador KJ, May R. Fetal antiepileptic drug exposure and learning and memory functioning at 6 years of age: the NEAD prospective observational study. Epilepsy Behav 2019;92:154-164. doi:10.1016/j.yebeh.2018.12.031

47 Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol 2013;12(3):244-252. doi:10.1016/S1474-4422(12)70323-X

48 Marson A, Burnside G, Appleton R, et al. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet 2021;397(10282):1375-1386. doi:10.1016/S0140-6736(21)00246-4

49 Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369(9566):1016-1026. doi:10.1016/S0140-6736(07)60461-9

50 Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia 2013;54(1):141-155. doi:10.1111/epi.12028

51 Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362(9):790-799. doi:10.1056/NEJMoa0902014

52 Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study no. 264 Group. N Engl J Med 1992;327(11):765-771. doi:10.1056/NEJM199209103271104

53 Brigo F, Igwe SC, Lattanzi S. Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents. Cochrane Database Syst Rev 2021;1(1):CD003032. doi:10.1002/14651858.CD003032.pub5

54 Riss J, Cloyd J, Gates J, Collins S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. Acta Neurol Scand 2008;118(2):69-86. doi:10.1111/j.1600-0404.2008.01004.x

55 Jensen HS, Nichol K, Lee D, Ebert B. Clobazam and its active metabolite N-desmethylclobazam display significantly greater affinities for α_2- versus α_1-GABA(A)-receptor complexes. PLoS One 2014;9(2):e88456. doi:10.1371/journal.pone.0088456

56 Jamil A, Levinson N, Gelfand M, et al. Efficacy and tolerability of clobazam in adults with drug-refractory epilepsy. Neurol Clin Pract 2021;11(5):e669-e676. doi:10.1212/CPJ.0000000000000992

57 Gidal BE, DeCerce J, Bockbrader HN, et al. Gabapentin bioavailability: effect of dose and frequency of administration in adult patients with epilepsy. Epilepsy Res 1998;31(2):91-99. doi:10.1016/s0920-1211(98)00020-5

58 Asconapé J, Diedrich A, DellaBadia J. Myoclonus associated with the use of gabapentin. Epilepsia 2000;41(4):479-481. doi:10.1111/j.1528-1157.2000.tb00192.x

59 Rissardo JP, Medeiros Araujo de Matos U, Fornari Caprara AL. Gabapentin-associated movement disorders: a literature review. Medicines (Basel) 2023;10(9):52. doi:10.3390/medicines10090052

60 Kwan P, Brodie MJ, Kälviäinen R, et al. Efficacy and safety of pregabalin versus lamotrigine in patients with newly diagnosed partial seizures: a phase 3, double-blind, randomised, parallel-group trial. Lancet Neurol 2011;10(10):881-890. doi:10.1016/S1474-4422(11)70154-5

61 French J, Kwan P, Fakhoury T, et al. Pregabalin monotherapy in patients with partial-onset seizures: a historical-controlled trial. Neurology 2014;82(7):590-597. doi:10.1212/WNL.0000000000000119

62 Hirsch LJ, Weintraub D, Du Y, et al. Correlating lamotrigine serum concentrations with tolerability in patients with epilepsy. Neurology 2004;63(6):1022-1026. doi:10.1212/01.wnl.0000138424.33979.0c

63 Ramey P, Osborn M, Abou-Khalil B. Conversion from immediate-release to extended-release lamotrigine improves seizure control. Epilepsy Res 2014;108(9):1637-1641. doi:10.1016/j.eplepsyres.2014.08.004

64 Ramey P, Osborn MR, Lowen KM, Reed RC, Abou-Khalil B. Unexplained spikes in lamotrigine serum concentration: nonlinear elimination? Acta Neurol Scand 2017;135(2):240-246. doi:10.1111/ane.12588

65 Hirsch LJ, Arif H, Nahm EA, et al. Cross-sensitivity of skin rashes with antiepileptic drug use. Neurology 2008;71(19):1527-1534. doi:10.1212/01.wnl.0000334295.50403.4c

66 Biehl A, Taube M, Kotloski RJ, et al. Lamotrigine use and potential for adverse cardiac effects: a retrospective evaluation in a Veteran population. Epilepsy Behav 2023;149:109496. doi:10.1016/j.yebeh.2023.109496

67 Marson A, Burnside G, Appleton R, et al. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet 2021;397(10282):1363-1374. doi:10.1016/S0140-6736(21)00247-6

68 Brigo F, Ausserer H, Tezzon F, Nardone R. When one plus one makes three: the quest for rational antiepileptic polytherapy with supraadditive anticonvulsant efficacy. Epilepsy Behav 2013;27(3):439-442. doi:10.1016/j.yebeh.2013.03.010

69 Poolos NP, Warner LN, Humphreys SZ, Williams S. Comparative efficacy of combination drug therapy in refractory epilepsy. Neurology 2012;78(1):62-68. doi:10.1212/WNL.0b013e31823ed0dd

70 Piña-Garza JE, Schwarzman L, Wiegand F, Hulihan J. A pilot study of topiramate in childhood absence epilepsy. Acta Neurol Scand 2011;123(1):54-59. doi:10.1111/j.1600-0404.2010.01347.x

71 Kockelmann E, Elger CE, Helmstaedter C. Significant improvement in frontal lobe associated neuropsychological functions after withdrawal of topiramate in epilepsy patients. Epilepsy Res 2003;54(2-3):171-178. doi:10.1016/s0920-1211(03)00078-0

72 Lee S, Sziklas V, Andermann F, et al. The effects of adjunctive topiramate on cognitive function in patients with epilepsy. Epilepsia 2003;44(3):339-347. doi:10.1046/j.1528-1157.2003.27402.x

73 Van Marter LJ, Pennell PB, Brown C, et al. Neonatal outcomes in the MONEAD study of pregnant women with epilepsy. J Pediatr X 2021;7:100073. doi:10.1016/j.ympdx.2021.100073

74 Bromley R, Adab N, Bluett-Duncan M, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev 2023;8(8):CD010224. doi:10.1002/14651858.CD010224.pub3

75 Bjørk MH, Zoega H, Leinonen MK, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol 2022;79(7):672-681. doi:10.1001/jamaneurol.2022.1269

76 Azar NJ, Bangalore-Vittal N, Arain A, Abou-Khalil BW. Tiagabine-induced stupor in patients with psychogenic nonepileptic seizures: nonconvulsive status epilepticus or encephalopathy? Epilepsy Behav 2013;27(2):330-332. doi:10.1016/j.yebeh.2013.02.016

77 Koepp MJ, Edwards M, Collins J, Farrel F, Smith S. Status epilepticus and tiagabine therapy revisited. Epilepsia 2005;46(10):1625-1632. doi:10.1111/j.1528-1167.2005.00263.x

78 Cerulli Irelli E, Cocchi E, Morano A, et al. Levetiracetam vs lamotrigine as first-line antiseizure medication in female patients with idiopathic generalized epilepsy. JAMA Neurol 2023;80(11):1174-1181. doi:10.1001/jamaneurol.2023.3400

79 Privitera M. Efficacy of levetiracetam: a review of three pivotal clinical trials. Epilepsia 2001;42(Suppl 4):31-35.

80 Kapur J, Elm J, Chamberlain JM, et al. Randomized trial of three anticonvulsant medications for Status epilepticus. N Engl J Med 2019;381(22):2103-2113. doi:10.1056/NEJMoa1905795

81 Makke Y, Abou-Khalil B. Brivaracetam efficacy and safety in focal epilepsy. Expert Rev Neurother 2019;19:955-964.

82 Strzelczyk A, Kay L, Bauer S, et al. Use of brivaracetam in genetic generalized epilepsies and for acute, intravenous treatment of absence status epilepticus. Epilepsia 2018;59(8):1549-1556. doi:10.1111/epi.14476

83 Ben-Menachem E, Mameniškienė R, Quarato PP, et al. Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies. Neurology 2016;87(3):314-323. doi:10.1212/WNL.0000000000002864

84 Klein P, McLachlan R, Foris K, et al. Effect of lifetime antiepileptic drug treatment history on efficacy and tolerability of adjunctive brivaracetam in adults with focal seizures: post-hoc analysis of a randomized, placebo-controlled trial. Epilepsy Res 2020;167:106369. doi:10.1016/j.eplepsyres.2020.106369

85 Klein P, Schiemann J, Sperling MR, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia 2015;56(12):1890-1898. doi:10.1111/epi.13212

86 Hirsch M, Hintz M, Specht A, Schulze-Bonhage A. Tolerability, efficacy and retention rate of Brivaracetam in patients previously treated with levetiracetam: a monocenter retrospective outcome analysis. Seizure 2018;61:98-103. doi:10.1016/j.seizure.2018.07.017

87 Yates SL, Fakhoury T, Liang W, et al. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. Epilepsy Behav 2015;52(Pt A):165-168. doi:10.1016/j.yebeh.2015.09.005

88 Aicua-Rapun I, André P, Rossetti AO, et al. Intravenous brivaracetam in status epilepticus: correlation between loading dose, plasma levels and clinical response. Epilepsy Res 2019;149:88-91. doi:10.1016/j.eplepsyres.2018.12.001

89 Villanueva V, Rodriguez-Osorio X, Juiz-Fernández Á, et al. Real-life evidence about the use of intravenous brivaracetam in urgent seizures: the BRIV-IV study. Epilepsy Behav 2023;147:109384. doi:10.1016/j.yebeh.2023.109384

90 Vossler DG, Knake S, O'Brien TJ, et al. Efficacy and safety of adjunctive lacosamide in the treatment of primary generalised tonic-clonic seizures: a double-blind, randomised, placebo-controlled trial. J Neurol Neurosurg Psychiatry 2020;91(10):1067-1075. doi:10.1136/jnnp-2020-323524

91 Sake JK, Hebert D, Isojärvi J, et al. A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. CNS Drugs 2010;24(12):1055-1068. doi:10.2165/11587550-000000000-00000

92 Husain AM, Lee JW, Kolls BJ, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Ann Neurol 2018;83(6):1174-1185. doi:10.1002/ana.25249

93 Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: a systematic review and network meta-analysis. Epilepsy Behav 2019;101(Pt B):106466. doi:10.1016/j.yebeh.2019.106466

94 Panda PK, Panda P, Dawman L, Sharawat IK. Efficacy of lacosamide and phenytoin in status epilepticus: a systematic review. Acta Neurol Scand 2021;144(4):366-374. doi:10.1111/ane.13469

95 Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. Epilepsia 1998;39(1):5-17. doi:10.1111/j.1528-1157.1998.tb01268.x

96 Kuchenbuch M, Lo Barco T, Chemaly N, Chiron C, Nabbout R. Fifteenyears of real-world data on the use of vigabatrin in individuals with infantile epileptic spasms syndrome. Epilepsia 2024;65(2):430-444. doi:10.1111/epi.17808

97 Kälviäinen R, Nousiainen I, Mäntyjärvi M, et al. Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. Neurology 1999;53(5):922-926. doi:10.1212/wnl.53.5.922

98 Toggweiler S, Wieser HG. Concentric visual field restriction under vigabatrin therapy: extent depends on the duration of drug intake. Seizure 2001;10(6):420-423. doi:10.1053/seiz.2000.0527

99 French JA, Krauss GL, Wechsler RT, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy A randomized trial. Neurology 2015;85:950-957.

100 Trinka E, Alsaadi T, Goji H, et al. Perampanel for the treatment of people with idiopathic generalized epilepsy in clinical practice. Epilepsia 2023;64(8):2094-2107. doi:10.1111/epi.17631

101 Ettinger AB, LoPresti A, Yang H, et al. Psychiatric and behavioral adverse events in randomized clinical studies of the noncompetitive AMPA receptor antagonist perampanel. Epilepsia 2015;56(8):1252-1263. doi:10.1111/epi.13054

102 Andres E, Kerling F, Hamer H, Kasper B, Winterholler M. Behavioural changes in patients with intellectual disability treated with perampanel. Acta Neurol Scand 2017;136(6):645-653. doi:10.1111/ane.12781

103 Faught E, Laliberté F, Wang Z, et al. Health care resource utilization before and after perampanel initiation among patients with epilepsy in the United States. Epilepsia 2017;58(10):1742-1748. doi:10.1111/epi.13857

104 Morgan CL, Varga S, Tsong W, Jenkins-Jones S, Holden S. Healthcare utilization and associated costs following initiation of perampanel in patients with epilepsy. Epilepsy Behav 2020;110:107137. doi:10.1016/j.yebeh.2020.107137

105 Blickhan M, Intravooth T, Staack AM, et al. Clinical experience of abrupt discontinuation of perampanel: a case series. Epileptic Disord 2021;23(1):148-152. doi:10.1684/epd.2021.1242

106 Canafoglia L, Barbella G, Ferlazzo E, et al. An Italian multicentre study of perampanel in progressive myoclonus epilepsies. Epilepsy Res 2019;156:106191. doi:10.1016/j.eplepsyres.2019.106191

107 Crespel A, Gelisse P, Tang NPL, Genton P. Perampanel in 12 patients with Unverricht-Lundborg disease. Epilepsia 2017;58(4):543-547. doi:10.1111/epi.13662

108 Dirani M, Nasreddine W, Abdulla F, Beydoun A. Seizure control and improvement of neurological dysfunction in Lafora disease with perampanel. Epilepsy Behav Case Rep 2014;2:164-166. doi:10.1016/j.ebcr.2014.09.003

109 Goldsmith D, Minassian BA. Efficacy and tolerability of perampanel in ten patients with Lafora disease. Epilepsy Behav 2016;62:132-135. doi:10.1016/j.yebeh.2016.06.041

110 Perez DQ, Espiritu AI, Jamora RDG. Perampanel in achieving status epilepticus cessation: a systematic review. Epilepsy Behav 2022;128:108583. doi:10.1016/j.yebeh.2022.108583

111 Hussein Z, Majid O, Boyd P, et al. Intravenous perampanel as an interchangeable alternative to oral perampanel: a randomized, crossover, phase I pharmacokinetic and safety study. Clin Pharmacol Drug Dev 2022;11(7):878-888. doi:10.1002/cpdd.1107

112 Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia 2017;58(9):1586-1592. doi:10.1111/epi.13852

113 Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376(21):2011-2020. doi:10.1056/NEJMoa1611618

114 Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378(20):1888-1897. doi:10.1056/NEJMoa1714631

115 Thiele EA, Bebin EM, Bhathal H, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol 2021;78(3):285-292. doi:10.1001/jamaneurol.2020.4607

116 Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2018;391(10125):1085-1096. doi:10.1016/S0140-6736(18)30136-3

117 Szaflarski JP, Devinsky O, Lopez M, et al. Long-term efficacy and safety of cannabidiol in patients with treatment-resistant epilepsies: four-year results from the expanded access program. Epilepsia 2023;64(3):619-629. doi:10.1111/epi.17496

118 Kühne F, Becker LL, Bast T, et al. Real-world data on cannabidiol treatment of various epilepsy subtypes: a retrospective, multicenter study. Epilepsia Open 2023;8(2):360-370. doi:10.1002/epi4.12699

119 Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15(3):270-278. doi:10.1016/S1474-4422(15)00379-8

120 Szaflarski JP, Bebin EM, Comi AM, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. Epilepsia 2018;59(8):1540-1548. doi:10.1111/epi.14477

121 Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy Behav 2018;86:131-137. doi:10.1016/j.yebeh.2018.05.013

122 Lattanzi S, Trinka E, Zaccara G, et al. Adjunctive cenobamate for focal-onset seizures in adults: a systematic review and meta-analysis. CNS Drugs 2020;34(11):1105-1120. doi:10.1007/s40263-020-00759-9

123 Schuetz E, Wagner K, Metternich B, et al. Effects of cenobamate on cognitive performance of epilepsy patients. Seizure 2022;102:129-133. doi:10.1016/j.seizure.2022.10.004

124 Catalán-Aguilar J, Hampel KG, Cano-López I, et al. Prospective study of cenobamate on cognition, affectivity, and quality of life in focal epilepsy. Epilepsia Open 2024;9(1):223-235. doi:10.1002/epi4.12857

125 Sperling MR, Klein P, Aboumatar S, et al. Cenobamate (YKP3089) as adjunctive treatment for uncontrolled focal seizures in a large, phase 3, multicenter, open-label safety study. Epilepsia 2020;61(6):1099-1108. doi:10.1111/epi.16525

126 Krauss GL, Klein P, Brandt C, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol 2020;19(1):38-48. doi:10.1016/S1474-4422(19)30399-0

127 Abou-Khalil B, Aboumatar S, Klein P, et al. Efficacy of cenobamate for uncontrolled focal seizures in patients with previous epilepsy-related surgery: post hoc analysis of a phase 3, multicenter, open-label study. Epilepsy Res 2022;184:106952. doi:10.1016/j.eplepsyres.2022.106952

128 Gogou M, Cross JH. Fenfluramine as antiseizure medication for epilepsy. Dev Med Child Neurol 2021;63(8):899-907. doi:10.1111/dmcn.14822

129 Polster T. Individualized treatment approaches: fenfluramine, a novel antiepileptic medication for the treatment of seizures in Dravet syndrome. Epilepsy Behav 2019;91:99-102. doi:10.1016/j.yebeh.2018.08.021

130 Knight EMP, Amin S, Bahi-Buisson N, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol 2022; 21(5):417-427. doi:10.1016/S1474-4422(22)00077-1

131 Gesche J, Cornwall CD, Delcomyn L, Rubboli G, Beier CP. Pseudoresistance in idiopathic/genetic generalized epilepsies - definitions, risk factors, and outcome. Epilepsy Behav 2022;130:108633. doi:10.1016/j.yebeh.2022.108633

132 Linane A, Lagrange AH, Fu C, Abou-Khalil B. Generalized onset seizures with focal evolution (GOFE) - a unique seizure type in the setting of generalized epilepsy. Epilepsy Behav 2016;54: 20-29. doi:10.1016/j.yebeh.2015.10.005

133 Lamy F, Valenti-Hirsch MP, Gauer L, et al. Genetic generalized epilepsy and generalized onset seizures with focal evolution (GOFE). Epilepsy Behav Rep 2022;19:100555. doi:10.1016/j.ebr.2022.100555

134 Gambardella A, Tinuper P, Acone B, et al. Selection of antiseizure medications for first add-on use: a consensus paper. Epilepsy Behav 2021;122:108087. doi:10.1016/j.yebeh.2021.108087

135 Hakeem H, Alsfouk BAA, Kwan P, Brodie MJ, Chen Z. Should substitution monotherapy or combination therapy be used after failure of the first antiseizure medication? Observations from a 30-year cohort study. Epilepsia 2023;64(5): 1248-1258. doi:10.1111/epi.17573

136 Semah F, Thomas P, Coulbaut S, Derambure P. Early add-on treatment vs alternative monotherapy in patients with partial epilepsy. Epileptic Disord 2014;16(2):165-174. doi:10.1684/epd.2014.0650

137 Talha Özgün O, Kandemir Yılmaz M, Mert Atmaca M, et al. Efficacy and tolerability of immediate switch from sodium channel blockers to lacosamide. Epilepsy Behav 2023;145:109355. doi:10.1016/j.yebeh.2023.109355

138 Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord 2014; 16(4):409-431. doi:10.1684/epd.2014.0714

139 Kwan P, Brodie MJ, Laurenza A, FitzGibbon H, Gidal BE. Analysis of pooled phase III trials of adjunctive perampanel for epilepsy: impact of mechanism of action and pharmacokinetics on clinical outcomes. Epilepsy Res 2015;117:117-124. doi:10.1016/j.eplepsyres.2015.09.002

140 Margolis JM, Chu BC, Wang ZJ, Copher R, Cavazos JE. Effectiveness of antiepileptic drug combination therapy for partial-onset seizures based on mechanisms of action. JAMA Neurol 2014;71(8):985-993. doi:10.1001/jamaneurol.2014.808

141 Lattanzi S, Canafoglia L, Canevini MP, et al. Adjunctive brivaracetam in focal epilepsy: real-world evidence from the BRIVAracetam add-on First Italian netwoRk STudy (BRIVAFIRST). CNS Drugs 2021;35(12):1289-1301. doi:10.1007/s40263-021-00856-3

142 Verrotti A, Lattanzi S, Brigo F, Zaccara G. Pharmacodynamic interactions of antiepileptic drugs: from bench to clinical practice. Epilepsy Behav 2020;104(Pt A):106939. doi:10.1016/j.yebeh.2020.106939

143 Stafstrom CE. Mechanisms of action of antiepileptic drugs: the search for synergy. Curr Opin Neurol 2010;23(2):157-163. doi:10.1097/WCO.0b013e32833735b5

144 Pisani F, Oteri G, Russo MF, et al. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. Epilepsia 1999; 40(8):1141-1146. doi:10.1111/j.1528-1157.1999.tb00832.x

145 Kinirons P, McCarthy M, Doherty CP, Delanty N. Predicting drug-resistant patients who respond to add-on therapy with levetiracetam. Seizure 2006;15(6):387-392. doi:10.1016/j.seizure.2006.05.001

146 Legge AW, Detyniecki K, Javed A, et al. Comparative efficacy of unique antiepileptic drug regimens in focal epilepsy: an exploratory study. Epilepsy Res 2018;142:73-80. doi:10.1016/j.eplepsyres.2018.03.011

147 Lattanzi S, Trinka E, Striano P, et al. Cannabidiol efficacy and clobazam status: a systematic review and meta-analysis. Epilepsia 2020;61(6): 1090-1098. doi:10.1111/epi.16546

148 Stephen LJ, Sills GJ, Brodie MJ. Lamotrigine and topiramate may be a useful combination. Lancet 1998;351(9107):958-959. doi:10.1016/S0140-6736(05)60613-7

149 Osborn M, Abou-Khalil B. The cenobamate-clobazam interaction- evidence of synergy in addition to pharmacokinetic interaction. Epilepsy Behav 2023;142:109156. doi:10.1016/j.yebeh.2023.109156

150 Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol 2018;75(3):279-286. doi:10.1001/jamaneurol.2017.3949

151 Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 2007; 62(4):375-381. doi:10.1002/ana.21064

152 Patsalos PN, Spencer EP, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs in epilepsy: a 2018 update. Ther Drug Monit 2018;40(5):526-548. doi:10.1097/FTD.0000000000000546